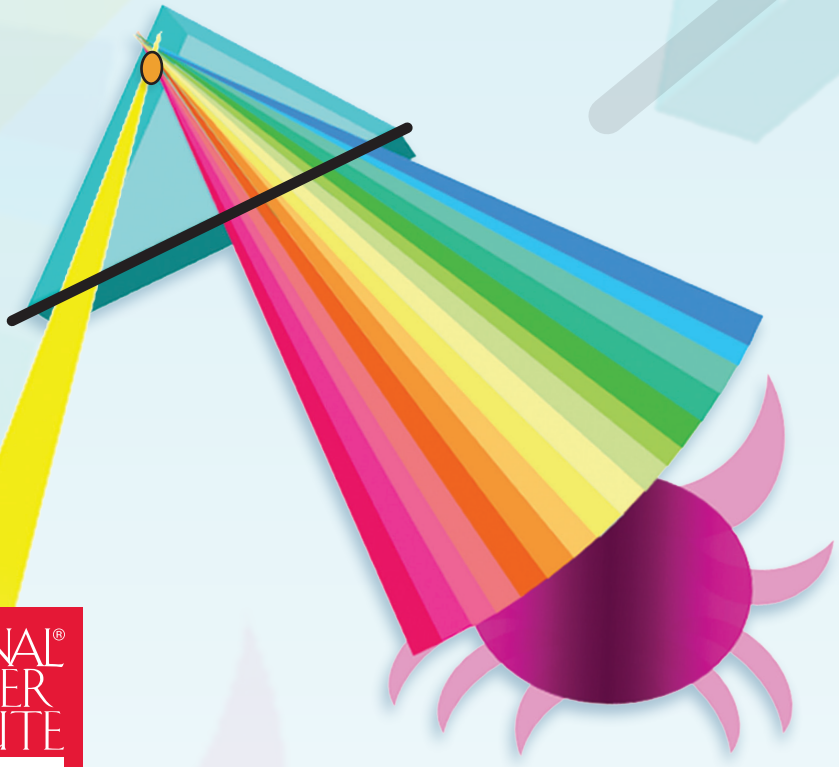
National Cancer Institute

Cancer Detection and Diagnostics Technologies for Global Health

August 22–23, 2011

NIH campus, Rockville, Maryland



NATIONAL® CANCER INSTITUTE

Technologies to overcome global healthcare disparities

Conference sponsored by the **National Cancer Institute**

http://www.cancer.gov

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES • National Institutes of Health

Table of Contents

Welcome to the Cancer Detection and Diagnostics Technologies for Global Health conference, sponsored by the Fogarty International Center (FIC) and the National Cancer Institute (NCI).

Cancer is emerging as a leading cause of death in poorer countries where the majority of the world's population lives. Moving cancer treatment to global health settings has been seen as costly, challenging or even hopeless, so relatively little effort has been devoted to this problem. However, early detection may lead to more affordable and effective cancer treatment so new diagnostics technologies have the potential to help overcome global healthcare disparities for cancer.

Most current technologies for cancer detection and diagnostics are not suitable for low income, low resource countries, but there is no concerted and coordinated effort to developing more appropriate technologies for widespread global health use. This conference represents an organized effort to discuss and demonstrate new, low-cost technologies with potential for cancer detection and diagnostics in low resource countries

During the conference, 27 speakers from academia, clinical centers, government and non- government organizations will be addressing a broad array of topics including:

- Global cancer burden
- Solid, hematologic, and infection-related cancers
- Research and research training efforts and needs
- Detection and sensor technologies
- Telemedicine and imaging technologies

In addition, the conference includes a poster session and an interactive technology demonstration session in which 25 novel and emerging prototypes of biodetection technologies will be presented.

The goals of this conference are to bring together cancer clinicians, researchers, engineers, and public health experts from academia, clinical centers, government, and non-governmental organizations to discuss the state of the science, focusing on clinical aspects of cancer and on promising technological developments for diagnosis, prognosis and treatment.

The NCI and FIC are committed to advancing public health and cancer research and we hope that the conference will be a venue to facilitate new scientific collaborations and interactions, build new research and research training programs in the field, and promote the translation of basic research to clinical applications in global heath settings, with the goal of reducing cancer-related health disparities in low to mid-resourced global settings

The conference organizing committee

Barbara A. Conley, MD*, Cancer Diagnosis Program*
Lalitha Shankar, MD, Ph.D, *Cancer Imaging Program*
Houston Baker, Ph.D, *Cancer Imaging Program*
Mukesh Verma, Ph.D, *Epidemiology and Genetics Research Program*
Paul Wagner, Ph.D, *Cancer Biomarkers Research Group*
Wendy Wang, Ph.D, *Cancer Biomarkers Research Group*
Ben Prickril, Ph.D, *NCI, International Center*
Yvonne Njage, M.D., *Fogarty International Center*
Ivan Ding, MD PhD, *Translational Research Program*
Avi Rasooly, Ph.D. *Cancer Diagnosis Program*

Cancer Detection and Diagnostics Technologies for Global Health

August 22-23, 2011

Natcher Auditorium, NIH campus– Building 45
Bethesda, Maryland

AGENDA (DRAFT)

Monday, August 22, 2011

7:00 a.m. – 3 p.m. **Registration**

Opening Session (Conley)

8:00 – 8:15 **Welcome: Douglas Lowy**, *National Cancer Institute*

8:15 – 8:30 **Opening Remarks: Barbara Conley,** *National Cancer Institute*

8:30 – 9:15 **Keynote address: Felicia Knaul,** *Harvard Global Equity Initiative,* Expanding Access to Cancer Care and Control in Lower and Middle Income Countries (LMICs): Promoting Equity and Strengthening Health Systems

Session I: Cancers throughout the world (Harford)

9:15 – 9:45 **Ahmedin Jemal,** *American Cancer Society*, An Overview of Global Cancer Incidence and Mortality Patterns

9:45– 10:15 **Jacqueline Sherris**, *PATH,* Innovative responses to global health challenges

10:15 – 10:45 **Joe Harford,** *NCI,* Breast Cancer Early Detection in Low-Resource Settings: What We Have Just Isn't Good Enough

10:45-11:15 **Clement Adebamowo**, *University of Maryland*, Cancer Management in Low Resource Countries

11:15 - 11:45 **Panel Discussion: Cancer in Global Health Settings (Harford)**

11:45 – 12:45 **Lunch (on your own)**

Session II: Solid cancers in global health settings (Conley and Trimble)

12:45 – 1:15 **Edward L. Trimble**, *National Cancer Institute*: Gynecologic Cancers: Ovarian and Cervical Cancer

1:15 – 1:45 **Benjamin Anderson,** *Fred Hutchinson Cancer Research Center*, Breast cancer management in the developing world

1:45 – 2:15 **Stephen Meltzer**, *Johns Hopkins University,* Gastrointestinal Malignancies

2:15 – 2:45 **Lewis Roberts,** *Mayo Clinic*, Hepatocellular Cancer

2:45– 3:00 **Break**

Session III Detection technologies for global health (Yager and Rasooly)

3:00 – 3:30 **Paul Yager**, *University of Washington,* Microfluidics 2.0: Dropping The Costs for Diagnostic Tests and Screening

3:30– 3:55 **Aydogan Ozcan,** *UCLA,* Photonics based Telemedicine Technologies toward Smart Global Health Systems

3:55– 4:20 **Michelle Khine**, *University of California Irvine,* Shrink-film Microfluidics for Inexpensive and Rapid Devices

4:20 – 4:45 **Fran Ligler**. *Navy Research Laboratory,* Optical Biosensors for Point-of-Care Diagnostics

4:45 – 5:10 **Panel Discussion: Detection and Diagnostics Technologies for Treatable Cancers in Global Health Settings (Conley, Trimble, Yager and Rasooly)**

5:20 – 7:00 p.m. **Meet and Greet Mixer / Technology Prototypes Demonstration and Poster Session**

Tuesday, August 23, 2011

7:00 – 3:00 p.m. **Registration**

8:00 – 8:15 **Opening Remarks: Ian Magrath,** *INCTR.* The International Network for Cancer Treatment and Research,

Session IV: Telemedicine and imaging technologies for global health (Garra and Shankar)

8:15 – 8:45 **Brian Garra**, *FDA***,** Ultrasound and Portable X-Ray Technology for Global Health

8:45 – 9:10 **Rebecca Richards-Kortum,** *Rice University,* Multi-Modal Optical Imaging to Improve Early Detection of Cancer in Low Resource Settings: Experience from China, India, Guatemala, and Botswana

9:10– 9:35 **Woonggyu Jung**, *University of Illinois,* Handheld Optical Imaging Scanner for Advanced Point of Care Diagnostics

9:35– 9:55 **Anuradha Godavarty**, *Florida International University*, Hand-held Optical Imaging Technology for Global Health and Breast Cancer

9:55 – 10:15 **Panel Discussion: Imaging for Treatable Cancers in Global Health Settings (Garra and Shankar)**

10:15-10:30 **Break**

Session V: Hematologic and infectious causes of cancers (Magrath and Verma)

10:30 – 11:00 **Ian Magrath,** *INCTR***,** Lymphoma

11:00– 11:30 **Gregory Reaman,** *FDA,* Childhood Leukemia

11:30 – 12:00 **Clement Adebamowo**, *University of Maryland,* HIV/AIDS-related Cancers

12:00 – 1:00 **Lunch (on your own)**

Session VI: sensors technologies for global health (Soper and Wagner)

1:00 – 1:30 **Steve Soper,** *Louisiana State University***,** Polymer-based Modular Microfluidic Point-Of-Care System for Automated Genotyping

1:30– 1:55 **Samuel Sia**, *Columbia University*, Microfluidics for Global Health Diagnostics

1:55– 2:20 **Shan Wang,** *Stanford University.* Bench Top and Handheld Magneto-Nanosensor Platform for Multivariate In Vitro Diagnostics of Cancer

2:20 –2:45 **Josh Balsam**, *FDA*, Webcam Biosensing for Point of Care Diagnostics

2:45– 3:10 **Haim Bau,** *University of Pennsylvania*, Molecular Diagnostics at the Point of Testing

3:10 – 3:30 **Panel Discussion: Detectors for Treatable Cancers in Global Health Settings (all Chairs)**

Speaker Biographies

Clement Adebamowo

Dr. Clement Adebamowo BM ChB Hons, FWACS, FACS, ScD is Director of Office of Strategic Information, Research and Training, Institute of Human Virology, Nigeria; President of the Society of Oncology and Cancer Research of Nigeria; Convener of the Nigerian Research Consortium; Director of the Center for Bioethics, Nigeria and of the West African Framework Program on Global Health and an Associate Professor of Epidemiology, University of Maryland, Baltimore. Dr. Adebamowo was until recently Professor of Surgery and Director of the Institute of Advanced Medical Training and Research at the University of Ibadan, Nigeria. In his new post as Director of Research for the Institute of Human Virology, Nigeria, Clement is managing the development of research infrastructure to take advantage of the programs for treatment and prevention of HIV/AIDS in Nigeria and a network of University Teaching Hospitals partners to develop research and training programs in Non Communicable Diseases Research and Clinical Trials while supporting the Communicable Diseases Treatment, Prevention and Research services of IHVN. Dr. Adebamowo studied medicine and surgery in Nigeria and, biostatistics and epidemiology in the United States. He is Honorary Professor, University of Dundee, UK; immediate past Chair of the International Affairs Committee of the American Society of Clinical Oncology; Chairman of the National Health Research Ethics Committee of Nigeria; Member of the Expert Advisory Panel on Clinical Practice Guidelines and Research Methods and Ethics of the World Health Organization (WHO); Country PI of the Partnership for Cohort Development and Training (PaCT); and Editor in Chief of Bioethics Online Journal (BeOnline®) and Cancer in Africa Online Journal (CIAO®). Clement is PI of 3 NIH-funded training programs and Co-Investigator on a fourth one. His research interests are Non Communicable Diseases Epidemiology, AIDS associated malignancies and Bioethics.

Benjamin Olney Anderson

Fred Hutchinson Cancer Research Center
Chair and Director, the Breast Health Global Initiative
Joint Full Member, Epidemiology, Division of Public Health Sciences

University of Washington School of Medicine
Professor of Surgery, Department of Surgery
Professor of Global Health – Medicine, Department of Global Health
Director, Breast Health Clinic, Seattle Cancer Care Alliance

Dr. Anderson is Professor of Surgery and Global Health Medicine at the University of Washington in Seattle where he has devoted his clinical practice to the care of patients with breast cancer and breast health issues. Dr. Anderson's clinical interests include oncoplastic surgery of the breast, the purpose of which is to improve oncologic and cosmetic outcome with complex breast cancer procedures. Dr. Anderson served as President of the American Society of Breast Disease (ASBD) from 2005 to 2007. He holds joint faculty positions in the Fred Hutchinson Cancer Research Center Division of Public Health Sciences and the University of Washington Department of Global Health. Dr. Anderson created and chairs the Breast Health Global Initiative (BHGI), the purpose of which is to develop and implement resource-sensitive, culturally appropriate guidelines for breast cancer early detection, diagnosis and treatment in low- and middle-income countries (LMCs). As private sector advisor on the U.S. delegation to the 58th World Health Assembly held in Geneva, Dr. Anderson contributed to the first WHO Approved Resolution on Cancer Prevention and Control passed in 2005, the purpose of which is to reinforce comprehensive cancer policies and strategies for LMCs. Most recently, Dr. Anderson was awarded the 2011 Partners in Progress Award by the American Society of Clinical Oncology (ASCO) for his commitment to women's health throughout the world and his dedicated efforts to improve their quality of care.

Joshua M. Balsam

Joshua is a mechanical engineering doctoral student at the University of Maryland, College Park, where he obtained his undergraduate degree in the same field in 2009.

As an undergraduate Joshua's research focused on nano-scale material structures and material processing under the advisement of Dr. Hugh A. Bruck. As a doctoral student, Joshua's research has branched out into the field of global health and point-of-care diagnostics (PoCD). This research is conducted full time at the White Oak research campus of the US Food and Drug Administration, where Joshua is engaged in the Medical Device Fellowship Program.

The primary objective of his research there is to investigate and develop new technologies and methods for low-cost PoCD. This includes lens-free optical detection, methods for employing low-cost sensor technology, and a novel method of Lab-on-a-Chip rapid prototyping. This research allows the FDA to more effectively understand and regulate new waves of PoC devices that are being developed by industry. It is also part of the body of work that will allow for truly affordable health care in resource-poor areas in the world.

Haim H. Bau

Haim H. Bau (PhD, Cornell, 1980) is a professor of Mechanical Engineering and Applied Mechanics at the University of Pennsylvania, Philadelphia. Haim's research interests are in micro and nanofluidics and nanotechnology. The Bau lab carries out fundamental research on multiphysics flow phenomena and biophysics. In addition, the lab develops devices for fundamental research as well as for diagnostics. Recently, the lab has developed a flow cell, dubbed the nanoaquarium, for electron microscope imaging of processes in liquid media as well as an assortment of microfluidic devices and processors for diagnostics at the point of care. For more information, see http://www.seas.upenn.edu/~bau/

Barbara A. Conley

Barbara A. Conley, M.D., is the Associate Director of the Cancer Diagnosis Program (CDP), National Cancer Institute. Her previous positions at NCI include Senior Investigator in the Clinical Investigation Branch, Chief of the CDP Diagnostics Research Branch, and Head, Aerodigestive Diseases in the intramural Medicine Branch. Immediately prior to her current appointment, she served as Chief, Division of Hematology/Oncology at Michigan State University (MSU). At MSU and the University of Maryland (1987-1997), Dr. Conley was the principal investigator on several NCI grants or contracts. Dr. Conley holds a B.S. from the University of Michigan and received her M.D. degree from Michigan State University. She is board-certified in Internal Medicine and Medical Oncology, and has research interests in diagnostic markers, drug development, and cancers of the aerodigestive tract. She has published extensively in many journals, and is on the editorial board of several professional publications.

Brian Garra

Dr. Garra completed his residency training at the University of Utah and spent three years as an Army radiologist in Germany before returning to Washington DC and the National Institutes of Health in the mid 1980's. After four years at the NIH, he joined the faculty of Georgetown University as Director of Ultrasound. In 1998, he left Georgetown to become Professor & Vice Chairman of Radiology at the University of Vermont/Fletcher Allen Healthcare. In 2009, Dr Garra returned to the Washington DC area as Chief of Imaging Systems & Research in Radiology at the Washington DC Veterans Affairs Medical Center. In April 2010, he also joined the FDA as Associate Director in the Division of Imaging and Applied Mathematics/OSEL. His time is currently split between VA and FDA activities.

His clinical interests include vascular ultrasound, GU ultrasound and breast ultrasound. His research interests include PACS, digital signal processing, quantitative ultrasound including Doppler, and ultrasound elastography. He was chair of the FDA radiological Devices Panel from 1999 to 2002 and has been involved in the approval of several new technologies including high resolution breast ultrasound, the first digital mammographic system, the first computer aided detection system for mammography, and the first computer aided nodule detection system for chest radiographs as well as the ultrasound contrast agent albunex. He also led the team that developed the AIUM breast ultrasound accreditation program, and helped develop the ARDMS registry in breast ultrasound. He co-founded the non-profit organization Imaging the World dedicated to placing small ultrasound systems with trained operators in small villages worldwide. He is currently working on new applications of elastography, poroelastic imaging, ultrasound simulation systems for training.

Anuradha Godavarty

Anuradha Godavarty received a Ph.D. in chemical engineering from Texas A&M University, College Station, Texas, USA in 2003. She worked as a Post-Doctoral Associate in the Department of Computer Science, University of Vermont, Burlington, Vermont in 2003-2004. She started as an Assistant Professor in the Department of Biomedical Engineering at Florida International University, Miami, Florida since 2004. Currently, she is an Associate Professor in the same department and university since 2010.Her research interests are in developing near infrared hand-held optical imaging technologies and applying them towards breast cancer imaging and functional brain mapping. To date, she has published her research in 30 peer-reviewed journals, and presented her work at various national/international conferences/scientific meetings. Dr. Godavarty has been recognized twice by the Miami Chamber of Commerce as a finalist for the Health Care Heroes Award (2010 and 2011) in the biomedical category for her work in the area of hand-held optical imager for breast cancer imaging.

Joe B. Harford

Director, Office of International Affairs
National Cancer Institute, National Institutes of Health
Bethesda, MD 20892
Email: harfordj@nih.gov

Dr. Joe Harford received a Ph.D. in Biochemistry from the University of Maryland Medical School and conducted basic research in molecular biology and cell biology. Dr. Harford has published over 100 scientific papers. Dr. Harford is one of the founding editors for *Current Protocols in Cell Biology*.

In 1993, Dr. Harford became the chief scientist for RiboGene, Inc., a biotechnology company where he managed four drug discovery programs in infectious diseases. From 1996 to1999, Dr. Harford served as Chairman of the Scientific Advisory Board of RiboGene, Inc, and served in a similar capacity for SynerGene Therapeutics, Inc., an early-stage biopharmaceutical company that focuses on molecular therapeutics for cancer. Dr. Harford is a co-inventor on two issued U.S. patents related to drug discovery. In 1996, Dr. Harford returned to the NIH where he served as Associate Director of the NCI and Chief of Staff of the Office of the Director.

In July 2002, Dr. Joe Harford was named Director of the Office of International Affairs of the National Cancer Institute. In this capacity, he has responsibility for a number of bilateral and multilateral interactions between the NCI and foreign cancer research institutions and other foreign entities. Dr. Harford serves as the Chair of the Strategic Advisory Group of the Ireland-Northern Ireland-NCI Cancer Consortium and as NCI liaison to the Middle East Cancer Consortium, the US-Japan Cooperative Cancer Research Program, the African Organization for Research and Training in Cancer, the American-Russian Cancer Alliance, and the International Network for Cancer Treatment and Research. Dr. Harford has represented the United States to the Governing Council of the WHO's International Agency for Research on Cancer and represented NIH for two years as a member of the Board of Trustees of the Human Frontier Science Program, an international non-governmental, nonprofit association devoted to the promotion of basic research. In July 2006, Dr. Harford was named as Strategic Leader for Knowledge Transfer by the International Union Against Cancer (UICC). In 2008, UICC altered its committee structure, and Dr. Harford was named to the UICC Board of Directors (NCI Liaison), the Solidarity Fund Taskforce, the Childhood Cancer Taskforce, and the Strategic Coordinating Committee. Dr. Harford has been appointed by the Irish Minister for Health and Children to the National Expert Group on Cancer Biobanking.

In 2007, Dr. Harford was recognized by the Arab Medical Association Against Cancer with an award, the citation os which reads "In recognition for his significant contribution to enhance the status of cancer care and cancer research in the region and for his unwavering efforts to support needed infrastructure and create opportunities in cancer education, training and capacity building to help cancer patients and their families throughout the Arab world."

Ahmedin Jemal

Dr. Ahmedin Jemal is Vice President of Surveillance Research program, National Home Office, American Cancer Society. He holds an adjunct appointment in the Department of Epidemiology, Emory University. Dr. Jemal's main research interests are in descriptive epidemiology of cancer (national and international patterns), in cancer disparities, and in using cancer surveillance data to accelerate the application of existing cancer control knowledge into practice.

Woonggyu Jung

Woonggyu Jung received his Ph. D. in 2008 from the Department of Biomedical Engineering at the University of California, Irvine. From 2001 to 2008, he worked at the Beckman Laser Institute and Medical Clinic at UC Irvine, which is one of the world's top research organizations in laser treatment and diagnosis. He currently is a postdoctoral researcher at the Beckman Institute for Advanced Science and Technology at the University of Illinois at Urbana-Champaign since January 2009.

Dr. Jung has a strong research background in optical imaging technologies including optical coherence tomography (OCT), multiphoton microscopy (MPM), and miniaturized optical imaging probes. His research interest is to develop new optical technologies that address challenges in clinical medicine and basic biological research. His long-term goal is to pursue implementation of research tools for *in vivo* translational studies, where functionalities such as real-time measurement, compactness and portability are essential. In previous work, he developed a successful platform of probe-based compact optical imaging systems for *in vivo* translational research, and has published more than 30 peer-reviewed journal papers in the field of biophotoics.

Michelle Khine

Michelle Khine is currently an Assistant Professor of Biomedical Engineering, Mechanical Engineering, Chemical Engineering and Materials Science at UC Irvine and scientific founder of Shrink Nanotechnologies (Carlsbad, Ca). She was an Assistant & Founding Professor at UC Merced ('06-'09). Michelle received her BS and MS from UC Berkeley in Mechanical Engineering ('99 and '01, respectively) and her PhD under Luke P Lee in Bioengineering ('05) from UC Berkeley and UCSF. She co-founded Fluxion Biosciences (South San Francisco, Ca) while in graduate school. Michelle was the recipient of the TR35 Award and named one of Forbes '10 Revolutionaries' in 2009 and by Fast Company Magazine as one of the '100 Most Creative People in Business' in 2011. Most recently, she was awarded the NIH New Innovator's Award.

Felicia Knaul

Felicia Knaul, MA, PhD (Economics, Harvard University), is Associate Professor at Harvard Medical School and Director of the Harvard Global Equity Initiative where she serves as the Secretariat for the Global Task Force on Expanded Access to Cancer Care and Control in Developing Countries.

She holds visiting academic appointments at the National Institute of Public Health of Mexico, and the Mexican Health Foundation where she has led a research group focused on health and the economy since 2000. Dr. Knaul is a board member of numerous organizations including: the Union for International Cancer Control; the Jalisco Cancer Institute; and the Sheikh Mohammed Hussein Al-Amoudi Center of Excellence in Breast Cancer in Saudi Arabia. She has held senior government posts at the Ministries of Education and Social Development in Mexico and at the Department of Planning in Colombia. She has also worked for several bilateral and multilateral agencies including WHO. In 2006, she was awarded the Global Development Network Prize for research in health.

After being diagnosed with breast cancer in 2007, Dr. Knaul founded Cáncer de Mama: Tómatelo a Pecho a Mexican non-profit association that promotes research, advocacy, awareness, and early detection initiatives for breast cancer in Latin America. She has published several articles on the topic of breast cancer in low- and middle-income countries in academic journals, lectures extensively on the topic both from the point of view of a patient-advocate and a researcher in health systems, and her experience has been written up in magazines including Science. Her book, Tómatelo a Pecho, released in October of 2009, recounts her personal experience with breast cancer and as founder of the program.

Dr. Knaul is Canadian, and resides in Boston and Mexico City. She and her husband, Dr. Julio Frenk, have two children, Hannah and Mariana Havivah.

Frances S. Ligler

Frances S. Ligler is the Navy's Senior Scientist for Biosensors and Biomaterials and a member and past chair of the Bioengineering Section of the National Academy of Engineering. She earned a B.S. from Furman University and both a D.Phil. and a D.Sc. from Oxford University. Currently working in the fields of biosensors and microfluidics, she has also performed research in biochemistry, immunology, and proteomics. She has over 350 full-length publications and patents, which have led to eleven commercial biosensor products and have been sited over 7500 times. She is the winner of the Navy Superior Civilian Service Medal, the National Drug Control Policy Technology Transfer Award, the Chemical Society Hillebrand Award, the Navy Merit Award, the Naval Research Laboratory (NRL) Technology Transfer Award, three NRL Edison Awards for Patent of the Year, the Furman University Bell Tower and Distinguished Alumni of the 20th Century Awards, and the national Women in Science and Engineering (WISE) Outstanding Achievement in Science Award. She serves as an Associate Editor of Analytical Chemistry and on editorial/advisory boards for Biosensors & Bioelectronics, Analytical Bioanalytical Chemistry, Sensors, Open Optics, and Applied Biochemistry and Biotechnology. Elected an SPIE Fellow in 2000, she also serves on the organizing committee for the World Biosensors Congress and the permanent steering committee for Europt(r)odes, the European Conference on Optical Sensors. In 2003, she was awarded the Homeland Security Award (Biological, Radiological, Nuclear Field) by the Christopher Columbus Foundation and the Presidential Rank of Distinguished Senior Professional by President Bush.

Douglas R. Lowy

Dr. Douglas Lowy is Deputy Director of the National Cancer Institute (NCI), National Institutes of Health (NIH), and Chief of the Laboratory of Cellular Oncology in the Center for Cancer Research at NCI. He received his medical degree from New York University School of Medicine, and trained in internal medicine at Stanford University and dermatology at Yale. Dr. Lowy's research includes the biology of papillomaviruses and the regulation of normal and neoplastic growth. The papillomavirus research is carried out in close collaboration with Dr. John Schiller, with whom he has co-authored more than 100 papers over the past 25 years. In the 1980s, they studied the genetic organization of papillomaviruses and identified the oncogenes encoded by the virus. More recently, they have worked on papillomavirus vaccines and the papillomavirus life cycle. Their laboratory was involved in the initial development, characterization, and clinical testing of the preventive virus-like particle-based HPV vaccines that are now used in the two FDA-approved HPV vaccines. Dr. Lowy's growth regulation research includes prior studies that established the importance of the ras gene family in cancer and the main mechanisms by which the NF1 tumor suppressor gene regulates normal cell growth. His growth regulation research is now focused primarily on the DLC family of tumor suppressor genes and their mechanism of action. Dr. Lowy is a member of the National Academy of Sciences (NAS) and also a member of the Institute of Medicine of the NAS.

Ian T. Magrath

Ian Magrath received his qualifications in medicine from the University of London. He holds a higher doctoral degree in Medicine and is a Fellow of the Royal College of Physicians and the Royal College of Pathologists. He has a special interest in the pathogenesis and treatment of non-Hodgkin's lymphomas, stemming from early in his career when he spent 2 years as Director of the Lymphoma Treatment Center in Kampala (University of Makerere), Uganda. He subsequently joined the National Cancer Institute (NCI), Bethesda, Maryland, and became Chief of the Lymphoma Biology Section of the Pediatric Oncology Branch, where his work was focused on the treatment and molecular pathogenesis of B cell lymphomas, particularly Burkitt's lymphoma, as well as the role of Epstein-Barr virus in the pathogenesis of the latter disease. During the last 35 years, he has had a particular interest in cancer control in developing countries and has been involved in the conduct of cancer control projects, clinical trials and basic research in many parts of the world, including India, Pakistan, Nepal, China, Mexico, Argentina, Brazil, Turkey, Tanzania, Kenya, Nigeria and Egypt. This led to his present position as President of the International Network for Cancer Treatment and Research (INCTR) in Brussels (in 2000), although he retains a position at the NCI. Dr Magrath is also adjunct Professor of Pediatrics at the Uniformed Services University of the Health Sciences in Bethesda, Maryland. He has authored over 360 original articles, chapters, reviews, commentaries and editorials relating primarily to the pathogenesis and treatment of malignant lymphomas, pediatric cancers, cancer in developing countries and Epstein Barr Virus. He has also edited several books, including "New Directions in Cancer Treatment," "The Non-Hodgkin's Lymphomas" (now in its 3rd edition as "the Lymphoid Neoplasms"), and "Gene Therapy." He serves or has served on several international committees and advisory boards for a number of organizations, including the World Health Organization, the International Atomic Energy Agency (PACT), the European School of Oncology, the International Union for Cancer Control and the American Association for Cancer Research. He has won a number of awards for his work and been invited to give several special lectures at major meetings of professional societies or Universities.

Selected Publications:

1. Magrath, Ian (Ed). The Lymphoid Neoplasms. Third Edition. Arnold Hodder, London, 2010
2. Magrath I. Lessons from clinical trials in African Burkitt lymphoma. Current Opinion in Oncology, 2009, 21:462–468.
3. Gascoyne RD, Magrath IT and Sehn L. Burkitt lymphoma. In Armitage J, Mauch PM, Harris NL, Coiffier B, Dalla-Favera R. Non-Hodgkin lymphomas. Kluwer W. Philadelphia, pp 334-357, 2009
4. Magrath I. B-cell Lymphoma/Burkitt Lymphoma. In Pediatric Lymphomas. Weinstein H and Link M (Eds). 2006, 141-174. Springer-Verlag, Berlin, Heidelberg.

Stephen J. Meltzer

Stephen J Meltzer, M.D. attended the State University of New York at Binghamton, where he earned his undergraduate degree in music composition. He proceeded to obtain his M.D. degree at the State University of New York in Buffalo. He did his internal medicine internship at Tulane University in New Orleans, followed by his internal medicine residency at the University of Texas Medical Branch in Galveston, Texas. He received his Master of Music degree in music composition from the University Of Colorado School Of Music. He was also a Gastroenterology Fellow at the University of Colorado Center, Denver. He then returned to New York, where he worked as a Gastroenterology fellow, at the Lenox Hill Hospital, in New York, NY. He spent three years in Los Angeles, California, with part of that time as a Postdoctoral fellow, in the Johnsson Comprehensive Cancer Center, at the UCLA Center for Health Sciences, and the other as an Assistant Professor in Residence, in the Gastroenterology Division, at UCLA Center for Health Sciences. He would later move to Baltimore, Maryland, where he would spend 4 years as Assistant Professor, 4 years as Associate Professor, and 9 years as Professor of Medicine in the Gastroenterology Division at the University of Maryland School of Medicine. During that time, he also served as Director of the Aerodigestive Program and Associate Director for Core Sciences at the the Greenebaum Cancer Center at the University of Maryland, Baltimore. He is currently the Harry and Betty Myerberg/Thomas R. Hendrix Professor of Gastroenterology, in the Departments of Medicine and Oncology and a Member, of the Sidney Kimmel Comprehensive Cancer Center at The Johns Hopkins University School of Medicine. He is an accomplished and active gastroenterologist and a renowned expert on the molecular genetic and epigenetic basis of gastrointestinal cancer and precancer, with a special emphasis on lesions of the esophagus. He is one of the first investigators to discover microRNA alterations in esophageal cancer, as well as one of the earliest researchers to identify circulating (blood-based) biomarkers (such as anti-p53 antibodies, methylated DNA, and proteomic profiles) in esophageal adenocarcinoma patients. Dr. Meltzer recently served as the Director of the Core MicroRNA Microarray Laboratory in a multi-consortium study of microRNA biomarkers in prostate, lung, and esophageal cancers funded by the NCI's Early Detection Research Network (EDRN). He has also published papers on microRNA alterations and their downstream target messenger RNAs in cholangiocarcinoma, inflammatory bowel disease, and gastric cancer. He was elected member of the American Society for the Clinical Investigation (ASCI) and the Association of American Physicians (AAP). He possesses extensive experience in directing multi-center translational research, most recently in another published EDRN-supported study of epigenetic biomarkers for the prediction of esophageal neoplastic progression. Dr. Meltzer has had continuous federal funding for the past 18 years and operates a large laboratory that is fully equipped to apply state-of-art genetic and epigenetic methodologies. For the past 20 years, he has also continuously amassed a large repository of frozen tissues and blood specimens obtained from control subjects and patients with Barrett's esophagus, esophageal adenocarcinoma, colorectal cancer, and colorectal adenomas.

Aydogan Ozcan

Dr. Aydogan Ozcan received his Ph.D. degree at Stanford University Electrical Engineering Department in 2005. After a short post-doctoral fellowship at Stanford University, he is appointed as a Research Faculty Member at Harvard Medical School, Wellman Center for Photomedicine in 2006. Dr. Ozcan joined UCLA in the summer of 2007, where he is currently an Associate Professor leading the Bio- and Nano-Photonics Laboratory at the Electrical Engineering Department.

Dr. Ozcan holds 17 issued patents and another 12 pending patent applications for his inventions in nanoscopy, wide-field imaging, lensless imaging, nonlinear optics, fiber optics, and optical coherence tomography. Dr. Ozcan is also the author of one book and the co-author of more than 170 peer reviewed research articles in major scientific journals and conferences. In addition, Dr. Ozcan is the founder and a member of the Board of Directors of Microskia Inc., and is a member of the program committee of *SPIE Photonics West Conference, SPIE International Symposium on Defense, Security and Sensing,* as well as the *IEEE Photonics Society Annual Meeting*. He also serves as a panelist and a reviewer for *National Science Foundation, NIH* and for Harvard-MIT Innovative Technology for Medicine Program. Prof. Ozcan also served as the General co-Chair of 2010 IEEE Winter Topical Meeting on Advanced Imaging in BioPhotonics.

Prof. Ozcan received several major awards including the 2011 SPIE Early Career Achievement Award, 2010 NSF CAREER Award, the 2009 NIH Director's New Innovator Award, the 2009 Office of Naval Research (ONR) Young Investigator Award, the 2009 IEEE Photonics Society (LEOS) Young Investigator Award and the MIT's Technology Review TR35 Award for his seminal contributions to near-field and on-chip imaging, and telemedicine based diagnostics.

Prof. Ozcan is also the recipient of the 2010 National Geographic Emerging Explorer Award, the 2010 Bill & Melinda Gates Foundation Grand Challenges Award, the 2010 Popular Mechanics Breakthrough Award, the 2010 Netexplorateur Award given by the Netexplorateur Observatory & Forum in France, the 2010 PopTech Science and Public Leaders Fellowship, the 2010 USC's Body Computing Slam Prize, and the 2009 Wireless Innovation Award organized by the Vodafone Americas Foundation as well as the 2008 Okawa Foundation Award, given by the Okawa Foundation in Japan.

Prof. Ozcan was also selected as one of the top 10 innovators by the U.S. Department of State, USAID, NASA, and NIKE as part of the LAUNCH: Health Forum organized in October 2010.

Dr. Ozcan is a Senior Member of IEEE, and a member of LEOS, EMBS, OSA, SPIE and BMES.
http://innovate.ee.ucla.edu//prof.-ozcan-brief-biosketch.html

Gregory Reaman

Associate Director of Oncology Science (EOM)

Gregory H. Reaman, M.D. joined the Center for Drug Evaluation and Research, Office of New Drugs, U.S. Food and Drug Administration as the Associate Director of the Office of Oncology Drug Products in 2011. He is the Founding and Immediate Past Chair of the **Children's Oncology Group (COG)** having served in this capacity from 2000 through 2010. The COG is comprised of over 200 member institutions, dedicated to clinical, translational, and epidemiology research in childhood cancer.

Dr. Reaman is a Professor of Pediatrics at The George Washington University School of Medicine and Health Sciences and a member of the Division of Hematology-Oncology at the Children's National Medical Center in Washington, D.C., which he directed for more than 17 years and Executive Director Emeritus of the Center for Cancer and Blood Disorders.

Dr. Reaman serves or has served on the Editorial Boards of Leukemia, Journal of Clinical Oncology, Journal of Pediatric Hematology/Oncology, Pediatric Blood and Cancer, The Oncologist, Cancer, and Physicians Data Query (PDQ), National Cancer Institute as well as **www.PLWC.org** (People Living with Cancer, now Cancer.net). He has served as an Associate Editor of Cancer and Leukemia and Lymphoma. He held the position of Executive Director for Scientific and Medical Affairs for the National Childhood Cancer Foundation (NCCF) and was a member of its Board of Trustees. Previously, he served on the Board of Directors of the American Cancer Society and chaired its Task Force on Children and Cancer. Dr. Reaman served on the Board of Directors of the American Society of Clinical Oncology and has served on the ASCO Patient Education Committee, the Education and Program Committees, the Grant Selection Committee, Cancer Survivorship Committee, and was the Chair of the ASCO Membership and Audit Committees. Also, he was a member of the Food and Drug Administration's Oncologic Drugs Advisory Committee and has chaired its Pediatric Subcommittee. He was a member of the NIH Roadmap Working Group. He serves on the Scientific Steering Committee of the United Kingdom Children's Cancer and Leukemia Group, the External Advisory Board of the Cancer Treatment and Research Center at the University of Texas Health Science Center at San Antonio and is a Senior Advisor to the Middle East Childhood Cancer Alliance (MECCA).

Additionally, he is a member of the Alliance for Childhood Cancer, a member of the Data Safety Monitoring Board of the National Cancer Institute's Clinical Oncology Program, and a member of the NCI's Translational Research Working Group.

His research interests are in the biology and treatment of childhood acute leukemia and new drug development for pediatric cancers.

He is the author of more than 300 peer - reviewed manuscripts and 16 book chapters.

Rebecca Richards-Kortum

Rebecca Richards-Kortum is the Stanley C. Moore Professor of Bioengineering at Rice University. Previously, she held the Cockrell Family Chair in Engineering #10 and was a Professor of Biomedical Engineering at the University of Texas at Austin, where she was also a Distinguished Teaching Professor. After receiving a B.S. in Physics and Mathematics from the University of Nebraska-Lincoln in 1985, she continued her graduate work at the Massachusetts Institute of Technology, where she received an MS in Physics in 1987 and a PhD in Medical Physics in 1990. She joined the faculty in Bioengineering at Rice University in 2005 and served as Chair of Bioengineering from 2005-2008.

In addition to being named a Howard Hughes Medical Institute Professor in 2002 and 2006, her awards include election to the US National Academy of Engineering (2008); Presidential Young Investigator, National Science Foundation (1991), Presidential Faculty Fellow, National Science Foundation (1992); Becton Dickinson Career Achievement Award, Association for the Advancement of Medical Instrumentation (1992); Y.C. Fung Young Investigator Award, American Society of Mechanical Engineers (1999). In 2001, she was elected to the Academy of Distinguished Teachers at The University of Texas at Austin and received the Chancellor's Council Outstanding Teaching Award for 2002. In 2004, she was named a Piper Professor by the Minnie Stevens Piper Foundation, reflecting teaching excellence in the State of Texas. She received the Sharon Keillor Award for Women in Engineering Education (2004) and the Chester F. Carlson Award (2007), both from the American Society for Engineering Education. She was elected fellow of AAAS and of BMES in 2008, and received the IEEE Educational Activities Board Vice-President Recognition Award (2008). She served on the inaugural National Advisory Council for Biomedical Imaging & Bioengineering (NIBIB) for the National Institutes of Health.

Dr. Richards-Kortum's research group is developing miniature imaging systems to enable better screening for oral, esophageal, and cervical cancer and their precursors at the point-of-care. In collaboration with faculty at the UT MD Anderson Cancer Center, her group has carried out clinical trials of this technique involving over 2,000 patients in the US, India and Nigeria. Her group is developing contrast agents for in vivo molecular imaging of changes associated with precancer including expression of epidermal growth factor reception. More recently, her group has worked to integrate advances in nanotechnology and microfabrication to develop novel, low-cost sensors to detect infectious diseases at the point-of-care, including cryptosporidium, malaria, and Tuberculosis.

At Rice University, Dr. Richards-Kortum has worked to establish new educational programs in global health technologies. She founded the HHMI supported program Beyond Traditional Borders (BTB). The goal of this program is to encourage students from multiple backgrounds to think beyond geographic and disciplinary boundaries to solve challenges in global health. The program has led to the creation of a new undergraduate minor in global health technologies at Rice. Students in the minor engage in project based courses to solve problems contributed by partners in developing countries. Thus far, more than 300 students have participated in BTB design projects, resulting in 40 new designs, 2 provisional patent applications, and 2 invention disclosures. These designs have been used by healthcare providers in 14 international healthcare settings and have impacted the lives of over 13,000 clients. The efforts of two of her students were recently recognized by President Clinton at the closing plenary session of the inaugural meeting of Clinical Global Initiative–University. Through outreach to middle and secondary schools in Texas and in developing countries, a total of 54 teachers from 16 schools and universities have implemented BTB-designed materials, impacting 1,891 middle and secondary school students. This momentum will continue to spread through the establishment of Rice 360°: Institute for Global Health Technologies–a joint effort with the Clinton Global Initiative to create a university-wide institute to develop and disseminate technologic and educational interventions to prevent disease in vulnerable populations.

Rebecca is married and has three sons, Alexander, Maxwell and Zachary and two daughters, Katie and Margaret.

Lewis R. Roberts

Professor of Medicine and Consultant, Division of Gastroenterology and Hepatology, Department of Medicine, Mayo Clinic.

President, Africa Partners Medical

Dr. Roberts earned his medical degree from the University of Ghana Medical School and a Ph.D. degree in Physiology and Biophysics from the University of Iowa. Subsequently, Dr. Roberts completed postgraduate medical training in Internal Medicine and Gastroenterology and Hepatology at Mayo Clinic. Dr. Roberts is a Fellow of the American College of Physicians, American Gastroenterological Association, American College of Gastroenterology, and the American Society for Gastrointestinal Endoscopy. He has received numerous awards, including the Mensah Sarbah Hall Prize for Academic Achievement from the University of Ghana, the Clinical Trainees Award for Distinguished Accomplishments in the Biomedical Sciences from the National Institutes of Health, the New Investigator Award from the Department of Medicine, Mayo Clinic, the Humanitarian Award from the Ghana Physicians and Surgeons Foundation, and the Paul Harris Fellowship from the Rotary International Foundation.

Dr. Roberts's clinical practice interests focus on liver and bile duct cancers and gastrointestinal endoscopy. His research interests include studies of the molecular mechanisms of liver carcinogenesis; development of biomarkers and clinical tests to improve the diagnosis and treatment of liver, bile duct, and pancreas cancers; and improvements in prevention, diagnosis and treatment of hepatitis and liver cancer in Africa as well as in immigrant African communities in the United States. Dr. Roberts's research has been funded by the National Institutes of Health, The Robert Wood Johnson Foundation, and the Foundation for Digestive Health and Nutrition. He has authored numerous articles, book chapters, abstracts and letters.

Dr. Roberts actively participates in institutional, national and international educational activities as a lecturer and mentor. Dr. Roberts serves as President of Africa Partners Medical, a non-profit organization focused on improving healthcare delivery in Africa through medical education, practical skills training, and provision of medical equipment and supplies.

Jacqueline Sherris

Vice President, Global Programs, PATH

Dr. Sherris is PATH's vice president of Global Programs. She oversees PATH's global programs and facilitates articulation of program strategies, fosters program collaboration and synergy, models management and performance leadership, and ensures effective program planning, evaluation, and impact assessment across the organization. Dr. Sherris also serves on PATH's Executive Leadership Team and represents PATH domestically and internationally.

Dr. Sherris has more than 20 years of experience in public health. From 2002-2007 she served as PATH's program leader for the Reproductive Health Strategic Program, through which she led and expanded PATH's cervical cancer prevention work, including efforts to increase access to HPV vaccines in developing countries. Other areas of reproductive health work that grew under her leadership include contraceptive supply security, pharmacists and reproductive health, technologies and interventions for women dealing with the consequences of unprotected sex, and integration of family planning and HIV and AIDS services. Prior to taking on the reproductive health program leader responsibilities, she led various reproductive health projects and programs at PATH.

Before joining PATH in 1987, Dr. Sherris coordinated the University of Washington's Academic Programs for Teachers and was a staff associate with the Population Information Program at The Johns Hopkins University, where she authored several issues of *Populations Reports*.

A frequent author on international health, women's health, and cervical cancer prevention in the developing world, she is an affiliate faculty member at the University of Washington's School of Public Health and Community Medicine and serves on the External Advisory Board of that school. Dr. Sherris received her MS in biology and her PhD in science education from Purdue University.

Samuel Sia

Samuel Sia is an Associate Professor at the Department of Biomedical Engineering at Columbia University. His lab focuses on using microfluidics for global health diagnostics and for 3D tissue biology.

He obtained his B.S. in biochemistry at the University of Alberta (Edmonton, Canada), Ph.D. in Biophysics at Harvard University, and postdoctoral fellowship in Chemistry at Harvard University. He was a Howard Hughes Medical Institute Predoctoral Fellow, National Science and Engineering Council of Canada Predoctoral Fellow, and Canadian Institute of Health Postdoctoral Fellow. Since 2005, he has been a faculty member of Columbia University's Biomedical Engineering department. His lab's work has been supported by the NIH, NSF, Wallace H. Coulter Foundation, American Heart Association, World Health Organization. He has been named one of the world's top young innovators by MIT Technology Review, and one of 10 innovators in human health and sustainability by NASA. He is a founder of Claros Diagnostics, a venture capital-backed company that is developing novel point-of-care diagnostics products; the company's first microfluidics product for monitoring prostate cancer growth received European Union regulatory approval in 2010.

Edward L. Trimble

Following graduation from Harvard College and the Johns Hopkins University School of Medicine, Edward L. Trimble trained in obstetrics and gynecology at the Vanderbilt University Medical Center. He earned a master's degree in public health from the Johns Hopkins School of Hygiene and Public Health, then completed a fellowship in gynecologic oncology at Memorial Sloan-Kettering Cancer Center. He is board-certified in obstetrics and gynecology, as well as in gynecologic oncology, by the American Board of Obstetrics and Gynecology.

In 1991, he joined the National Cancer Institute, where he is now Head, Gynecologic Cancer Therapeutics and Quality of Cancer Care Therapeutics, Clinical Investigation Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis. His duties involve scientific liaison with the Gynecologic Oncology Group and the American College of Surgeons Oncology Group, as well as oversight of issues involving the elderly, minorities, women's health, international collaboration, cost, cancer health disparities, health-related quality of life and patient-reported outcomes in NCI-sponsored treatment trials. For his work at NCI he has received two Public Health Service Commendation Medals, 6 NIH Merit Awards, and the NCI Director's Gold Star Award.

In June 2011 Dr Trimble was appointed Acting Director of the NCI's new Center for Global Health by NCI Director Dr. Harold Varmus.

Shan X. Wang

Dr. Wang currently serves as the director of the Stanford Center for Magnetic Nanotechnology and a Professor of Materials Science & Engineering, jointly of Electrical Engineering at Stanford University, and by courtesy, a Professor of Radiology at Stanford School of Medicine. He is a Co-PI of the Stanford-led Center for Cancer Nanotechnology Excellence and Translation (CCNE-T). Dr. Wang specializes in Magnetic Nanotechnology, Biosensing, Spintronics, and Information Storag, and has published over 190 papers, and holds 28 patents (issued and pending) on these subjects. Dr. Wang contributed two books and four book chapters on magnetic biochip, nanoparticles, information storage, and embedded inductors, respectively, and gave more than 100 invited presentations in major scientific conferences and seminars around the globe, and his work received media coverage from ABC TV, Economist, San Jose Mercury News, Technology Review, EE Times, ScienceWatch, People's Daily and the like. Dr. Wang was an inaugural Frederick Terman Faculty Fellow at Stanford University (94-97), an IEEE Magnetics Society Distinguished Lecturer (2001-2002), and was elected an IEEE Fellow (2009). Prof. Wang received the Ph.D. in electrical and computer engineering from the Carnegie Mellon University (CMU) at Pittsburgh in 1993.

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[6] Gaster RS, Hall DA, Wang SX, Nano Lett., 11, 2579-2583, 2011.

Paul Yager

Paul Yager, a native of Manhattan, received his A.B. in Biochemistry from Princeton in 1975, and a Ph.D. in Chemistry from the University of Oregon in 1980. He specialized in vibrational spectroscopy of biomolecules, particularly phospholipids. He was an NRC Fellow at the Naval Research Laboratory in Washington, DC from 1980 to 1982, joining the NRL staff in 1982. At NRL he focused on self-assembly of lipid microstructures and the development of biosensor technologies. He joined the Department of Bioengineering at the University of Washington in Seattle in 1987 as Associate Professor. Initial projects included work on biosensors, the structure of silk, and use of lipid microstructures for controlled release of pharmaceuticals. He was promoted to Professor in 1995, becoming Vice Chair in 2001, Acting Chair in 2007 and Chair in 2008. He currently holds Adjunct faculty position in Chemistry, Chemical Engineering, Oral Biology and Global Health.

Since 1992, research in the Yager lab has focused on development of microfluidic devices for the manipulation of biological fluids and the monitoring of medically significant analytes. Support has been received from NSF, NIH, DARPA, The Whitaker Foundation, the government of Singapore, and private companies. Support from Senmed Medical Ventures and DARPA resulted in the creation, in 1996, of Micronics, Inc., a Redmond, WA-based company dedicated to microfluidic solutions for problems in the life sciences and medicine. The primary goal of current work in his laboratory is decentralization of biomedical diagnostic testing in the developed and developing worlds, with the aim of reducing the cost of healthcare. Yager is also active in efforts to promote better technology transfer at the University of Washington. In 2005 Yager was awarded a $15.4M grant from the Bill & Melinda Gates Foundation under their Grand Challenges in Global Health initiative; the DxBox project developed a low-cost rugged point-of-care platform based on microfluidics for diagnosing diseases in the developing world. Since 2008, the lab has had a growing focus on development of instrument-free medical diagnostics based on low-cost 2-dimensional paper networks. Specifics can be found at http://faculty.washington.edu/yagerp/.

Speaker Abstracts

Clement Adebamowo

Cancer management in low resource environments

Clement Adebamowo

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From a health systems perspective, the challenges facing cancer management in low resource environments (LRC) today is similar to those that faced those responding to the HIV/AIDS epidemic several years ago. These include shortages of appropriately trained manpower, optimal utilization of available manpower and infrastructure, missing linkages and referral systems, lack of community engagement, stigma, injustice, inequity, corruption, inadequate public health infrastructure, supply chain management and lack of political will. In a sense, compared to HIV infection which though multi-systemic in impact is a single disease, cancer consist of several diseases requiring multiple, deeper and different levels of resources for management and prevention.

These challenges while initially appearing daunting however represent a unique historic opportunity for the entire world to re-evaluate the medical and public health response to the cancer challenge. Whereas, it has been easy to identify the challenges to cancer management, the solutions are more elusive and in a sound-bite driven world, with a flavor-of-the-month mentality, the chronic persistent work required to respond to the cancer challenge may struggle for funding and attention. In this presentation, a construct which provides one approach to responding to the cancer challenge in LRC will be presented.

Benjamin O. Anderson

Breast Cancer Management in the Developing World

Benjamin O. Anderson, MD, FACS

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Globally, breast cancer is the most common cancer among women, comprising 23% of all female cancers that are newly diagnosed in more than 1.1 million women each year.[1] Breast cancer is the most common cause of cancer-related death among women worldwide, with case fatality rates highest in low- and middle-income countries (LMCs). Despite the common misconception that breast cancer is predominantly a problem of wealthy countries, 55% of breast cancer deaths each year in fact occur in developing rather than developed countries.[2] More than 411,000 deaths each year result from breast cancer annually, accounting for more than 1.6% of female deaths from all causes.[3] By 2010, the annual global burden of new breast cancer cases will rise to 1.5 million with an ever-increasing majority will be from LMCs.[2] Approximately 4.4 million women diagnosed with breast cancer in the last 5 years are currently alive, making breast cancer the single most prevalent cancer in the world.[1]

While evidence-based guidelines outlining optimal approaches to breast cancer detection, diagnosis, and treatment have been well developed and disseminated in several high-resource countries such as the U.S., these guidelines may be inappropriate to apply in LMCs for numerous reasons including inadequate personal resources, limited health care infrastructure, lack of pharmaceuticals, and cultural barriers. Hence, there is a need for clinical practice guidelines oriented toward LMCs, specifically considering and adapting to existing health care resources. The Breast Health Global Initiative (BHGI) has developed evidence-based, economically feasible, and culturally appropriate guidelines that can be used in nations with limited health care resources to improve breast cancer outcomes.[4] Modeled after the approach of the National Comprehensive Cancer Network (NCCN), BHGI created and applied a consensus panel process now formally endorsed by the Institute of Medicine (IOM)[5] to define resource-sensitive guidelines for breast cancer early detection,[6] diagnosis,[7] treatment,[8] and health care systems,[9] as related to breast health care delivery in LMCs. The BHGI guidelines are intended to assist ministers of health, policymakers, administrators, and institutions in prioritizing resource allocation as breast cancer treatment programs are implemented and developed in their resource-constrained countries.

Several key observations were made through the BHGI resource-stratified guidelines.[10] Breast cancer outcomes correlate with the degree to which 1) cancers are detected early, 2) cancers can be diagnosed correctly, and 3) proper multimodality treatment can be provided in a timely fashion.[11] Cancer prevention through health behavior modification may influence breast cancer incidence in LMCs.[12] Diagnosing breast cancer at earlier stages is predicted to reduce breast cancer mortality. Programs to promote breast self-awareness and clinical breast examination and resource-adapted mammographic screening are important early detection steps.[6] Screening mammography has been shown to reduce breast cancer mortality, but is cost prohibitive for most LMCs.[13, 14] Breast imaging, initially with ultrasound and, at higher resource levels with diagnostic mammography, improves preoperative diagnostic assessment and permits image-guided needle sampling.[7] Comprehensive multimodality treatment including surgery, radiation, and systemic drug therapies, must be in place for the benefit of early cancer detection to be realized.[8]

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Joshua Balsam

Webcam Biosensing for Global Health

Joshua Balsam

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To address the growing needs of global health, sensitive, low cost, simple, and portable medical diagnostic point of care detectors are needed. Many medical diagnostic assays are based on optical detection in devices that are suitable only for laboratory environments. We describe here a multi-wavelength fluorometer based on a simple, low cost (e.g., less than $10) webcam with sensitivity and capability similar or superior to several current commercial devices. These devices include a commercial plate reader (Tecan Infinite m1000), a micro-array reader (GenePix 4000B), and a fluorescent microscope.

The portable, battery-operated Webcam-based fluorometer system consists of five modules: (1) a CMOS Webcam to monitor light emission, (2) a stage used to perform plate assays, micro-array analysis, or microscopy, (3) filters and multi-wavelength LED or laser illuminator for fluorophore excitation, (4) a portable computer to acquire and analyze images, and (5) image stacking software for image enhancement.

For plate assays, webcam results were compared to results from a CCD astronomical camera and a plate reader using the same plate assay. Our data suggests that when used in a single frame mode, the CMOS webcam fluorometer limit of detection (LOD) is 1000 nM compared to a LOD of 30 nM for the CCD camera and 60 nM for the plate reader. However the use of the webcam in a video mode combined with image stacking enhancement enables the LOD to be reduced to 30nM, which is the same as the far more expensive (~100X) CCD camera. A schematic diagram and photograph of the device in this configuration can be seen in Figure 1.

The same webcam is also converted to a low cost florescent microscope with illumination at 390-650nm and with magnification of approximately 500X which can bring costly florescent microscopy to the global health setting.

The third application of the webcam is for microarray analysis. Microarrays are very large arrays of recognition ligands, such as oligonucleotide, cDNA, protein, peptide, antibody, carbohydrate, tissue, or aptamer, immobilized (chemically bonded) at defined locations on a solid matrix. Microarrays are primarily used for DNA analysis. Microarrays have a great potential for molecular diagnostics. The use of webcam based microarray reader may bring molecular diagnostics to the global health setting.

To make use of the webcam based detectors, we developed an array of Lab on a Chip (LOC) devices which enable a user to perform complex biological assays without a laboratory.

The data presented here suggest that the most basic, simple, and lowest cost webcam can provide sensitivity similar or superior to a sophisticated state-of-the-art plate reader, and thus may enable low cost, portable, point-of-care testing to be realized for various optical and fluorescent-based medical diagnostic assays to address mounting Global Health needs.

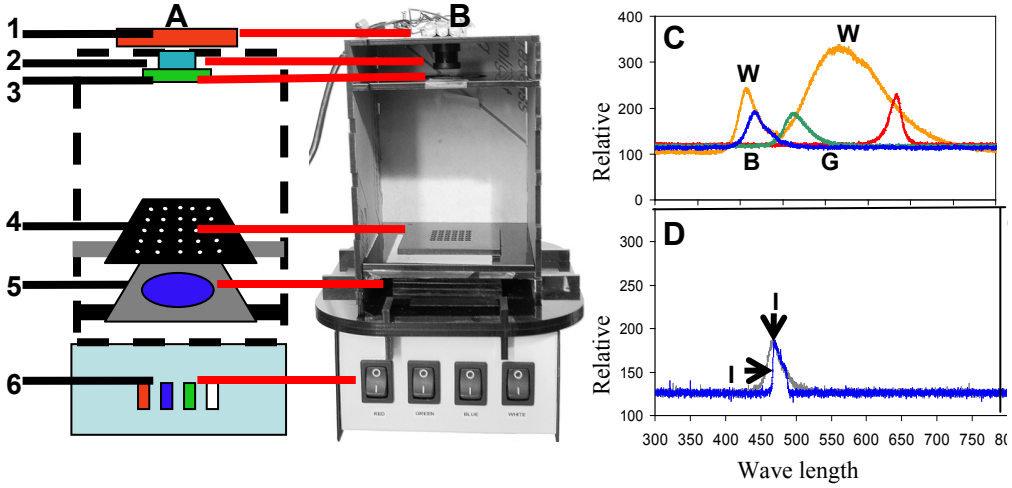

Figure 1: Webcam based plate assay fluorometer A). a schematic configuration of the Webcam based fluorometer with the main system components highlighted in the schematic: [1] a webcam camera mounted in a custom build acrylic box, [2] interchangeable lens with a green band pass emission filter [3] mounted on the end of the lens. Black acrylic sample chip [4]. Blue band pass excitation filter [5] and multi-wavelength LED [6]. B) a photo of a webcam based fluorometer**.** C). The excitation **s**pectra (measured by a spectrometer) of the multi-wavelength LED for the (W) white, (B) blue, green (G) and red (R) LED illumination. D). blue LED illumination spectra with (I) or without (II) blue filter.

Haim H. Bau

Molecular Diagnostics at the Point of Testing

Haim H. Bau*, Changchun Liu, and Michael Mauk

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In recent years, there has been a growing interest in point of care testing (PoCT) to provide health care personnel with timely information that facilitates informed decisions; to monitor spread of diseases and contaminants; and to make sophisticated capabilities available outside centralized laboratories such as in poor resource regions. Most efforts in the development of point of testing devices have focused on immunoassays. Advances in new isothermal amplification strategies enable one to develop molecular (nuclear acid-based) diagnostic tests that are just modestly more complicated than immunoassays, but provide much greater sensitivity and specificity. Here, we describe briefly some of the devices that have been developed and the experiments that were carried out at the Micro & Nano Fluidics Lab at the University of Pennsylvania.

The core component of our devices for molecular diagnostics is the integrated, multifunction, isothermal amplification chamber (**Fig. 1**). The amplification chamber (10-20µl volume) enables nucleic acid isolation, concentration, purification, amplification, and detection [1]. The amplification chamber stores encapsulated (thermally-released) dried reagents needed for DNA amplification [2]. When desired (i.e, in the case of low abundance analytes), the sample volume can far exceed the amplification chamber volume. The pre-stored reagents (not shown in **Fig. 1**) are released and hydrated, just in time, when the chamber's temperature exceeds ~55˚C. Arrays of amplification reactors can be accommodated on a single substrate to facilitate multi-analyte detection, control, and calibration. To amplify target nucleic acid sequences, we employed loop meditated amplification (LAMP) technology [3]. The devices can accommodate, however, other isothermal amplification schemes.

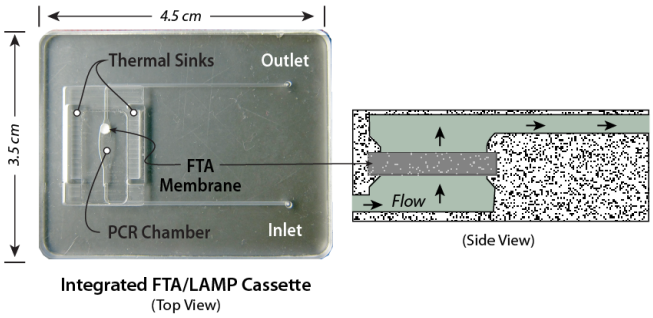

Fig. 1: A module (top view) containing a nucleic acid amplification reactor (left). A cross-section (right) showing sample flows through the isolation membrane.

To demonstrate the capabilities of the amplification reactor depicted in **Fig. 1**, we spiked HIV-1 virus in saliva samples taken from willing (healthy) volunteers [1] and E.-Coli in urine [4]. Our experimental set-up is shown in **Fig. 2**. The devices can operate with a simple processor that allows one to obtain quantitative data (**Fig. 2A and B**) or as completely un-instrumented, qualitative devices (**Fig. 2C and D**). The device shown in Fig. 2C is self-heated [5]. The heating is provided with an exothermic reaction, and the temperature is regulated with a phase change material. The amplicons are detected in real time with an intercalating dye (**Fig. 3A and C**). Alternatively, the amplification products can be discharged onto a lateral flow strip for detection. Our experiments consistently demonstrated a limit of detection better than 100 target molecules / ml sample.

We anticipate using the devices for, among other things, monitoring the viral load of patients undergoing HIV therapy, identifying drug-responsive and drug-resistant bacteria in stool, urine, and other body fluids, and monitoring the safety of food and water supplies. With modifications, the devices might be used to detect the presence of cancer cells in body fluids and to construct gene expression profiles.

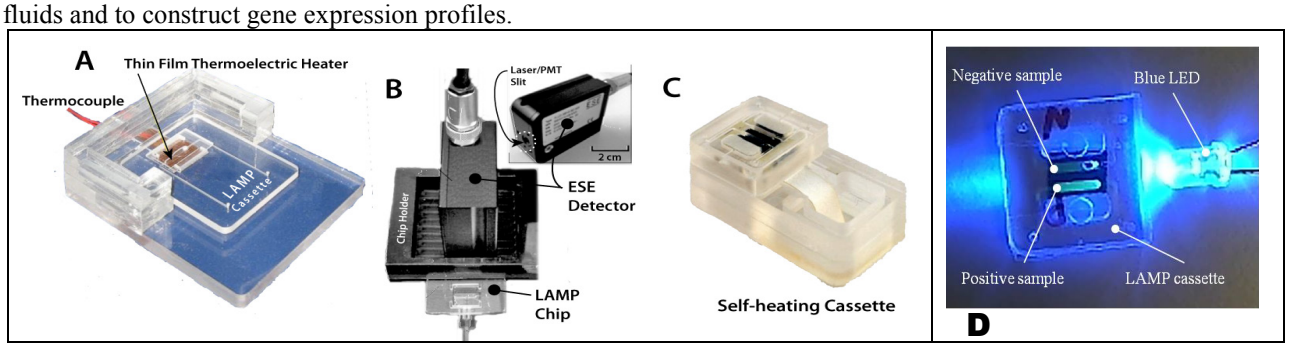

Fig. 2: The set-up used for proof of concept experiments. (A) Photograph of the processor for real-time amplification and detection with electrical heating. The cassette holder is equipped with a thin film resistance heater, a thermocouple,

and a seat for the detector [1,4,5]. (B) The fluorescent signal is excited and detected with a portable, compact (match-box size, Qiagen ESE Fluo Sens SD 003) optical reader. In the future, this reader may be replaced with a blue LED and a smart cell phone camera (see D). (C) Photograph of a cassette heated with a self-regulating exothermic reaction chamber (no electrical power is required) [5]. The amplification reactor is maintained at 60-65oC independent of the ambient temperatures. (D) Feasibility demonstration of monitoring fluorescent emission with a cell phone camera. The devices in (C) and (D) feature two reactors, but can contain an array of amplification reactors for concurrent detection of multiple pathogens and for control, calibration, and quantification.

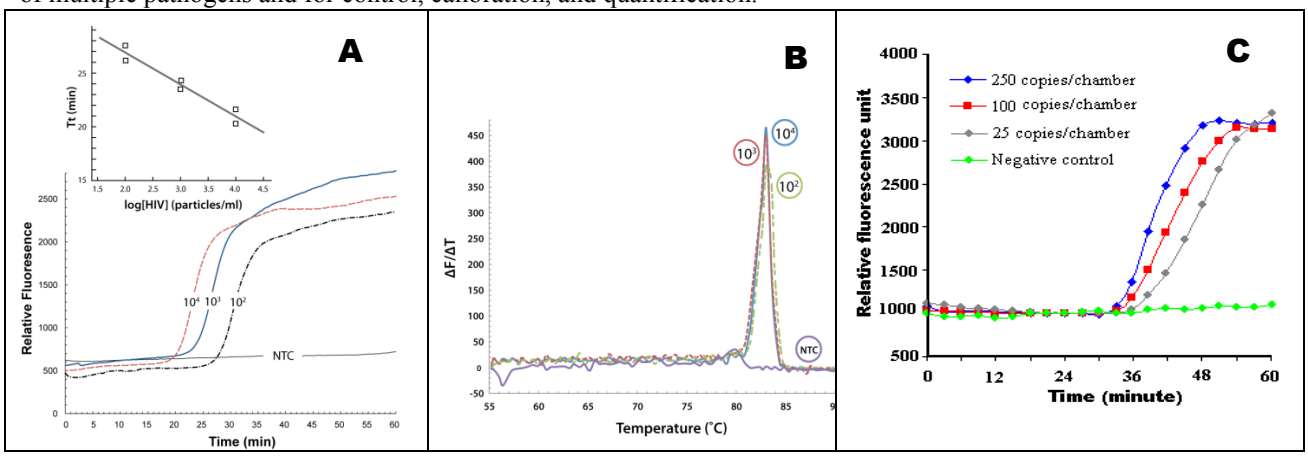

Fig. 3: (A) Real-time monitoring of Reverse Transcription LAMP of saliva samples laden with 10^4, 10^3, 10^2, and 0 (negative control) HIV particles / ml [1]. Inset: The threshold time Tt as a function of the HIV concentration (particles/ml). The threshold time is used to quantify the target concentration. (B) A melting curve: the derivative of the fluorescence intensity with respect to the temperature is depicted as a function of the temperature when the analyte consisted of 10^3, 10^2, 10 and 0 (negative control) HIV particles in the reaction chamber. The peak occurs at a melting temperature consistent with the length of the target amplicon. (C) Real time detection of Escherichia coli DNA in the LAMP cassette [4]. The experiments were carried out with cassettes similar to the ones in Fig. 1 and the set-up shown in Figs. 2 A and B. Similar performance was obtained with the self-heating device [5].

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Brian Garra

Imaging Communications and Education Technology for Global Health

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Deployment of diagnostic imaging systems to under-resourced environments requires proper communications and training infrastructure to be effective. There are many examples of imaging equipment sent to developing countries only to sit unused because these critical components were not included. For ultrasound, the equipment is inexpensive but traditional training of a person to perform imaging (a sonographer) requires six months to two years and is very expensive. Traditional training limited to one organ or one type of pathology can take less time but often requires the trainers to travel to remote areas where only a few can be trained at a time. This method is too labor intensive and costly to allow rapid deployment of ultrasound systems.

One alternative method is to employ electronic learning where modular courses are taken by trainees over the internet or from recorded DVD's. These would include training and test images and either on line or DVD based quizzes. Electronic learning can be enhanced further by the use of simulators that help train the prospective operator on machine operation and even the motions needed to properly manipulate an ultrasound transducer to create an image. An example of such an approach is the ultrasound e-learning system being developed by the World Federation of Ultrasound in Medicine and Biology[i]. Several ultrasound simulators have been commercially developed and one being tailored to a low resource environment is being developed at Worcester Polytechnic Institute[ii].

Another approach is to reduce the training burden by employing simplified ultrasound scanning methods that use technology to reduce the amount of training needed. The scan protocols employed by Imaging the World[iii] only require knowledge of external landmarks rather than internal anatomy and so can be taught in a few days. The resulting images are interpreted in a fashion similar to CT where the interpreter finds the organs and determines whether pathology is present or not. Scan protocols for the detection of thyroid cancer, neck adenopathy and breast cancer have been created and are being tested.

Training of operators for X-Ray and CT is less burdensome than that for ultrasound. A combination of on-line/DVD based training plus a short hands-on course should be sufficient. It is important for any system to have a way of monitoring the performance of trainees after completion of training. Periodic submission of cases to a review panel or random review of cases for quality assurance if the images are stored in a PACS network are effective solutions.

With increased numbers of diagnostic images comes the need to be able to transfer them to different locations for interpretation and treatment planning and monitoring. The most ubiquitous networks for transferring imagery are cell phone networks. These can be slow and unreliable so robust communications software capable of high levels of image compression must be employed. Video compression protocols are capable of high levels of compression and may be useful in some cases. Another network alternative is satellite based networks but use of such networks can be costly and may best be reserved for backup capability and emergency data communications. Each locale has its own specific problems and limitations and having a selection of usable technologies will help to ensure that a low cost effective solution can be used at each clinic or hospital where imaging is deployed.

[i] See the website: http://www.wfumb2009.com/session/407.asp 22 July 2011.

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[iii] Garra BS, DeStigter K, McEathron B, Dattamajumdar A, Widmer R, et. al. Scan Protocols for Use by Nonmedical Personnel in Developing Countries: Organ Visibility and Reproducibility evaluation. Presented at the 2008 Convention of the American Institute of Ultrasound in Medicine. 13 March 2008 San Diego, CA, USA

Anuradha Godavarty

Hand-Held Optical Imaging Technology

Dr. Anuradha Godavarty and Dr. Sarah J. Erickson

Device Description: Hand-held based optical imaging devices are recently developed which are portable and patient-comfortable. However, the NIR devices developed to date have not performed 3D tomography since they are unable to coregister the image to the tissue geometry. In our Optical Imaging Laboratory, we have developed a handheld optical imager which has automated coregistration facilities to enable 3D tomographic imaging. The device employs a flexible probe head that can contour to any tissue volume/curvature and image large tissue areas in near real-time to allow a functional (i) B-scan of the tissue (like an ultrasound), as well as (ii) 3D tomographic scan (like an MRI), upon employing the developed novel imaging approaches.

Principle of operation: The optical imaging technology utilizes non-ionizing near-infrared light to see few cm deep within the tissue and differentiate different tissue types (e.g. normal vs. diseased). The light is similar to that from a laser pointer.

The hand-held device (see Figure 1) works in conjunction with its proprietary coregistration software. It has been developed to image large tissue volumes using a flexible probe face that contours to different surface tissue curvatures. Because the device has a flexible head that contours, certain body parts can be better visualized in three dimensions. The three-dimensional (3D) tomographic ability of the device has been demonstrated on large tissue phantoms using a fluorescence-enhanced imaging technique. Simultaneous illumination and detection from multiple point locations is carried out to reduce the overall imaging time. The instrumentation can acquire both continuous wave (CW)–based and frequency domain–based optical measurements as required. Frequency-domain optical measurements provide more information about the tissue and also better depth information of the targets (or tumors) over the CW based measurements. CW based has a faster imaging time, making it a good clinical approach for near real-time imaging studies.

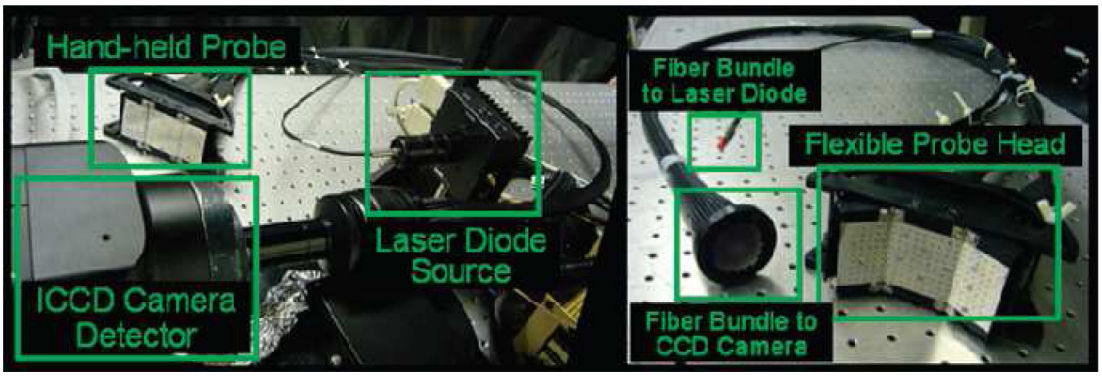

Figure 1. Handheld probe–based optical imaging system showing the handheld probe is fiber-optically coupled to the laser source and ICCD camera (left). The probe face is flexible to contour to different tissue curvatures (right).

In summary, the non-invasive hand-held optical device with the following features:

1. Flexibility to image any given tissue curvature and volume over larger surface areas
2. Portable device (see schematic in Figure 2) that can be available in a physician's office apart from radiology centers
3. Ability to perform near real-time imaging of large tissue areas for immediate results
4. Ability to perform both 2D surface as well as 3D mapping of tissue geometries in a matter of few seconds.
5. Capability to improve patient comfort from avoiding tissue compression (as in x-rays)
6. Ability to perform 3D volumetric analysis of imaged tissue geometries (e.g. tumor localization studies etc.)

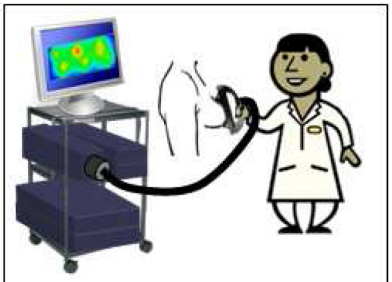

Figure 2 – Schematic of portable hand-held optical device.

The unique features of our device that do not exist in other handheld optical devices (in the absence of a second imaging modality) are highlighted in gray (see above).

Potential Utility of the Technology: The technology has multiple applications. The primary application of interest is breast cancer imaging at various stages of the disease (e.g. diagnosis, prognosis/tumor treatment response studies). The secondary indication for this technology will most likely be sports injuries or disease progression monitoring. Ankle injuries and concussions are few of the most common sports injuries where our device is expected to have important applications.

Other potential applications include:

- Sentinel Lymph Node mapping
- Function Brain Mapping in neurologically challenged populations (e.g. epilepsy, autism, cerebral palsy)
- Lie Detection Tool
- Drug delivery
- Any body tissue imaging (along curvatures)

Potential Applications for Global Health: Our technology has wide commercial applications (as listed above) across a multitude of industries on a global scale but as a starting point, our initial focus in breast cancer. Breast cancer affects approximately 1 in 8 women and is one of the leading causes of cancer related deaths for women in the industrialized world. Worldwide the diagnostic imaging market is $15.8 billion[1] and is expected to grow by six percent a year.[2] Specifically the U.S. market for mammography equipment sales was estimated at $339 million in 2002 with an expected compound annual growth rate of more than eight percent. Globally, mammography equipment sales are expected to grow at more than 20 percent per year[3], and reach $1.1 billion by 2015.

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Joe Harford

Breast Cancer Early Detection in Low-Resource Settings: What We Have Just Isn't Good Enough

Joe Harford

Director, Office of International Affairs, NCI

Breast cancer mortality rates in the U.S. dropped dramatically over a relatively short period (an approximate decrease of 24% between just 1990 and 2000). One estimate from the NCI-supported Cancer Intervention and Surveillance and Modeling Network based on of seven independent statistical models suggest that 28-65 percent (median = 46%) of the observed decrease in mortality can be attributed to screening with the remainder ascribed to adjuvant treatment. In a recent publication, the estimate of the contribution of mammography (in Norway) was estimated to be only at most 10% with the remainder of the ~28% observed decrease in mortality ascribed to a "time effect" presumed to be the result of increased breast-cancer awareness, improved therapy, and the use of more sensitive diagnostic tools that were occurring concurrently with implementation of mammographic screening. Despite the contribution of mammography to the decrease in breast cancer mortality in high-income countries, it is far from a perfect means of early detection. Not every breast carcinoma is detected by mammography, and not every death is averted even among those faithfully participating in a mammographic screening program. Indeed, we often forget that even if a mammographic screening program reduces mortality by 30% (likely an overestimate of screening's impact), this means that 7 of 10 of those who would have died without the program still die with it. Nonetheless, screen detected tumors tend to be smaller, well-differentiated and less likely to have regional lymph node involvement, factors that make treatment more efficacious and survival more likely. Smaller, lower stage tumors also impact treatment options (e.g., allowing for breast conserving surgery). In general, low- and middle-income countries (LMICs) have lower rates of breast cancer than do more industrialized countries of North America and Europe. These lower incidence rates mean that screening programs aimed at detecting early breast cancer in asymptomatic populations of women would have a lower "yield" i.e., significantly more women would need to be examined to find a *bona fide* case of breast cancer. For mammographic screening programs to be effective, infrastructure and trained personnel are required, and these simply do not currently exist in most LMICs. Mammographic screening programs and the follow-up procedures that they generate are also expensive and may simply be unaffordable in many LMICs where healthcare systems are already overburdened e.g., the U.S. Medicare reimbursement for a single screening mammogram is more than many LMICs spend per capita annually on all health issues combined. Because the average age of breast cancer in LMICs tends to be younger, it has been suggested that breast cancer screening programs begin at earlier age in these settings, a move that would lower yield and increase costs of a screening program since the younger average age of breast cancers in LMICs is predominantly driven by the age distribution of the population and relatively fewer older women with breast cancer rather than by higher age-specific incidence rates in younger women. Based on all of these considerations, it is suggested that existing resources in LMICs might better be used in raising awareness to encourage more women with palpable breast lumps to seek and receive treatment in a more timely matter instead of focusing on very large asymptomatic populations. All of these considerations also strongly suggest that more research is needed into more accurately predictive and cost-effective means for early detection and diagnosis of breast cancers in LMICs. Reference: Harford J.B.: Breast-cancer early detection in low-income and middle-income countries: do what you can versus one size fits all. Lancet Oncol. 12:306-12, 2011.

Ahmedin Jemal

An Overview of the Global Cancer Burden

Ahmedin Jemal, Melissa Center

Surveillance Research, American Cancer Society

The global burden of cancer continues to increase largely because of the aging and growth of the population, increases in incidence and death rates for cancers related to western behaviors, and lack of progress in reducing cancers related to infections in economically transitioning countries. Notably, rates for lung and colorectum cancers in a few of these countries have already surpassed those in the US and other western countries. Breast cancer now has replaced cervical cancer as the leading cause of cancer death among females in economically developing countries. Survival after a diagnosis of cancer is poorer in developing countries most likely because of late stage presentation and limited access to timely and standard treatment. A substantial proportion of the global burden of cancer could be prevented through the application of existing cancer control knowledge, including tobacco control policies, vaccination (for liver and cervical cancers) and early detection and treatment, as well as public health campaigns promoting physical activity and a healthier dietary intake. Public health professionals, policy makers, and donors can and should play a major role in accelerating the application of such interventions globally.

Woonggyu Jung

Handheld optical imaging scanner for advanced point of care diagnostics

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We demonstrated an advanced point-of-care handheld diagnostic instrument using optical coherence tomography (OCT) for use in a fast-paced clinical environment. This instrument enables the visualization of both surface and cross-sectional structure of various tissues of interest in screening and primary care such as the cornea, retina, tympanic membrane, and the skin, as well as practical functionalities for efficient diagnostic procedures. Our handheld optical imaging scanner is based on a pair of computer-controlled galvanometer-mounted mirrors, three different lens mounts, and miniaturized video camera. Interchangeable lens mounts were designed to conform to the outer shape of the ear and eye, as shown in Fig. 1(A). Lens mounts for ophthalmic and skin imaging include an eyecup for a comfortable interface with the human subject, and an easy approach to locate the focal position of the OCT beam. The ear lens mount was constructed by modifying the same metal ear tip used in existing commercial otoscopes. This allows for the use of disposable ear specula for each patient. Our handheld OCT scanner was integrated with a compact spectral-domain OCT system which uses a superluminescent diode (Superlum) having a 70 nm FWHM spectral bandwidth at the center wavelength of 830 nm, and a 140 kHz CMOS line scan camera (Basler) with 2048 pixels. The entire system was designed and equipped on a portable medical cart which is able to house the optical setup, computer, monitor, control units, and other accessories, as shown in Fig. 1(B) [1].

We acquired real-time 2-D OCT images from normal healthy volunteers and medical patients, under IRB-approved protocols. The entire imaging and diagnostic procedures using this handheld OCT scanner was efficient and straightforward. During the OCT imaging procedure using this handheld scanner, physicians readily found the region they wished to image, because the center of the video image was aligned with the lateral scanning path of the OCT beam [see Fig. 1(C)]. After the OCT imaging procedure, the physician was able to make direct comparisons using co-registered OCT and video images in both space and time. Fig. 2 shows representative OCT images of various tissues revealing detailed morphological structure.

Figure 1. (A) Photographs of a handheld OCT scanner and lens mounts. All lens mounts were packaged in threaded lens tubes for convenient interchange. (B) Photograph of cart based SD-OCT system accompanying the handheld scanner. The optical setup including spectrometer and reference optical path is contained on a 12″ × 18″ optical alignment board to fit within a small portable medical cart. The handheld scanner has a 2 m long optical and electrical cable, so the physician can easily access tissue sites on the patient. (C) Photograph of the OCT imaging procedure. The physician positions the handheld scanner at the tissue site, finds the desired imaging location, and clicks a save button mounted on handle of the scanner while monitoring both video and OCT images.

While this handheld OCT scanner can have an immediate impact in several major fields where OCT is becoming established (ophthalmology, dermatology, oncology), the greatest potential use of our scanner is likely to be in the primary and pediatric care offices as well as in the emergency room or the front-line of medical care, replacing the traditional yet technically simplistic ophthalmoscope and otoscope. Unlike the surface viewing ophthalmoscope and otoscope, our handheld scanner provides both surface and cross-sectional morphology of tissues in real time and *in vivo*. It offers the potential improvement of diagnostic ability for various diseases such as middle ear biofilms and infections, and diabetic retinopathy [2]. Even though this handheld OCT scanner was initially developed to be used in primary care medicine or similar medical services, its design and configuration can be easily modified and transformed for other medical applications requiring high resolution imaging of tissue and fast diagnostic feedback. Thus, the application of

this handheld scanner can be expanded to multiple stages of clinical care where point-of-care OCT can be applied and potentially used for screening, detecting, diagnosing, and monitoring disease. This has the potential to further enhance of the quality of healthcare as well as a bring time and cost advantage.

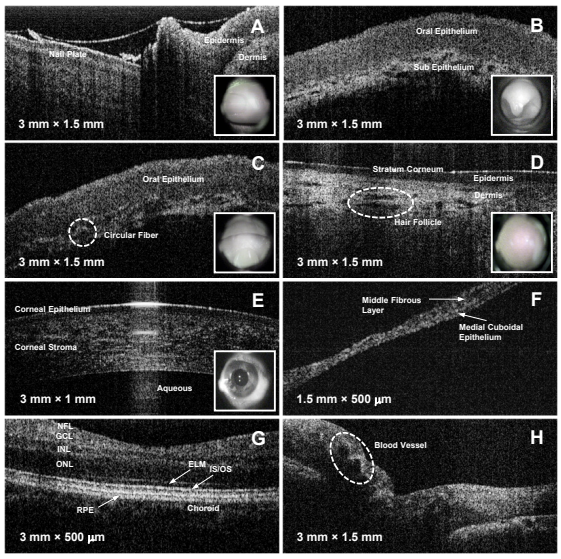

Figure 2. *In vivo* OCT and video images acquired from a normal human. (A) nail fold, (B) uvula, (C) gum, (D) arm, (E) cornea, (F) tympanic membrane, (G) retina around fovea, (H) retina around optic nerve head: NFL, nerve fiber layer; GCL, ganglion cell layer; INL, inner nuclear layer; ONL, outer nuclear layer; ELM, external limiting membrane; IS/OS, junction between the inner and outer segment of the photoreceptors; RPE, retinal pigment epithelium.

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Michelle Khine

Low Cost Substrate for Molecular Capture and Detection

The challenge of micro- and nano-fabrication lies in the difficulties and costs associated with patterning at such high resolution. Instead of relying on traditional fabrication techniques largely inherited from the semiconductor industry we have developed a radically different approach. We pattern at the large scale, which is easy and inexpensive, and rely on the heat-induced relaxation of pre-stressed polymer sheets – commodity shrink-wrap film – to achieve our desired structures. Using this approach, we have demonstrated that we can create fully functional and complete microfluidic devices with integrated nanostructures for molecular capture and sensing, printed electronics, and even optical components, all within minutes. These devices which can be use for biomedical assays cost only pennies to make and obviate the need for dedicated costly equipment. Because this process is compatible with roll-to-roll plastic processing, it is also scalable and cost-effective enough for point of care applications.

Felicia Knaul

Expanding Access to Cancer Care and Control in Lower and Middle Income Countries (LMICs): Promoting Equity and Strengthening Health Systems

Felicia Marie Knaul

Director, Harvard Global Equity Initiative and Secretariat to the Global Task Force on Expanded Access to Cancer Care and Control in Developing Countries; Founder, Cáncer de mama: Tómatelo a Pecho; and person living with cancer

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Once thought to be a problem primarily of the developed world, cancer is now a leading cause of death and disability in poorer countries, making it an unforeseen health priority and a leading New Challenge Disease (*NCD*). While developing countries account for the vast majority of deaths and of disability-adjusted life years lost in the world to the disease, they receive only 5% of global cancer resources.

Death and suffering from cancer is increasingly concentrated in LMICs. A prolonged and protracted cancer transition is occurring in LMICs that parallels what has been documented overall in health. Cancers of infectious origin or those for which prevention is possible are becoming diseases only of the poor; yet, these are not the only cancers of the poor as non-communicable diseases also present an emerging challenge. Further, the ratio of mortality to incidence, according to Globocan data, for any cancer that can be prevented or treated is substantially higher in poorer populations. In the case of childhood cancer, for example, the figure is just over 10% in Canada, compared to 90% in the 25 poorest countries. Closing the cancer divide is an equity imperative that should but does not figure high on global health agendas.

The myth that "nothing can be done to close the divide" is exactly that – a myth. Experience has shown that in resource-constrained countries without direct access to many specialized services, much can be done to prevent and treat cancer. Innovative delivery mechanisms utilize primary and secondary caregivers, as well as twinning and telemedicine to break down the many of the barriers of distance and human resource scarcity. Other strategies that can ameliorate the level of care in low resource settings include using of the array of off -patent drugs that have proven effective, as well as creating regional and global mechanisms for financing and procurement of drugs and other inputs. Furthermore, models for innovative financing also exist and several LMICs have included cancer treatment in national health insurance coverage with a focus on people living in poverty. These strategies can strengthen health systems to meet the challenge of cancer as well as many other diseases both chronic and acute.

GTF.CCC was convened in 2009 by several institutions based at Harvard University. This task force is composed of leaders from the global health and cancer care communities, and is dedicated to developing, implementing, and evaluating strategies to advance this agenda. The presentation includes elements of the GTF.CCC report that will be released in Fall of 2011.

Frances S. Ligler

Optical Biosensors and Systems Integration

Frances S. Ligler

Naval Research Laboratory, Washington, DC

New concepts for molecular recognition, integration of microfluidics and optics, simplified fabrication technologies, and improved approaches to biosensor system integration are producing smaller, faster, cheaper biosensors with capacity to provide effective and actionable information. We have combined microfluidic mixers, magnetic field control, and hydrodynamic focusing methods to move target molecules and cells into a variety of interrogation devices. These approaches achieve improved target delivery to sensors and reduced clogging. Most importantly, we have focused on issues critical for effective systems integration, including the interactivity of the choices for sampling technology, biochemistry, optics, fluidics, and electronics. The overall sensing geometry, size, power, and data readout must address the sensing needs and the user requirements—in a final format that is as simple, robust, and inexpensive as possible.

Ian Magrath

The International Network for Cancer Treatment and Research (INCTR)

Ian Magrath

President, Brussels

Because of the increasing importance of cancer as a global health problem, INCTR was established in Brussels in 1998 as an international non-profit organization (NGO) dedicated to building capacity for cancer treatment and research in developing countries. Its founder members were the UICC and Institute Pasteur (Brussels). Support for the project was approved by the NCI Executive Committee and funding was assigned by the then NCI Director, Dr. Richard Klausner. Since 2003, INCTR has interacted with NCI via the Office of International Affairs (Dr. Harford). INCTR partners with other major organizations, including the World Health Organization, IAEA's Program for Action in Cancer Therapy and the Union for International Cancer Control (UICC). Its major focus at present is cancer in women and children and hematological neoplasms. It functions through a series of INCTR-wide programs, including clinical trials, pathology, pediatric oncology, palliative care, oncology nursing, encouraging the development of the evidence base, and is about to initiate programs in adult oncology and psychosocial care. Each program includes a number of projects and is run by a director assisted by a small group of experts (faculty) who participate via on-site visits for assessment, education, audit or monitoring, or through helping to create or actively participating in web-based approaches to training and education. In addition to its programs, INCTR has branches (legally established non-profit entities) and offices (representation) in various countries. Branches in high income countries (USA, Canada, UK, France) help develop resources for projects and work on specific areas of interest relevant to INCTR's overall goals. Branches and Offices in developing countries (Brazil, Egypt, Nepal, Cameroon, Tanzania, India) participate in national or international projects as well as training and education of health professionals from their own country or nearby countries. A major strategy is to develop "reference centers" for improved diagnosis, delivery of patient care, education and research and to expand these to national or regional networks that will function as cooperative groups and/or training centers. Examples of centers that are actively involved in such activities include the pediatric cancer unit at the Muhimbili Hospital in Tanzania, the Black Lion Hospital in Ethiopia and the Palliative Care Unit at the MNJ cancer center in Hyderabad, India. INCTR has projects in breast cancer, screening and vaccination against cervical cancer, acute lymphoblastic leukemia and lymphomas, especially Burkitt lymphoma and HIV-associated lymphomas, Wilms' tumor, retinoblastoma, nasopharyngeal cancer. More information is available via its website at www.inctr.org.

Ian Magrath

Lymphomas

Ian Magrath

International Network for Cancer Treatment and Research, Belgium

Lymphomas are neoplasms of the immune system (innate and adaptive), i.e., of the system involved with protection against infection, foreign substances and probably tumors. Lymphomas can usually be related to a normal counterpart cell (e.g., small cell lymphoma, mantle cell lymphoma, marginal zone lymphoma, follicular lymphoma). They may appear anywhere in the body, but are most frequently associated with lymphoid aggregates, such as lymph nodes, spleen and mucosal lymphoid tissue. Some occur at extranodal sites, even where lymphoid tissue is not normally present - usually in response to chronic inflammation (e.g., MALT lymphomas). Lymphomas may also be associated with immunosuppressed states, such as HIV infection, inherited immunodeficiencies, or abnormal DNA repair. Lymphomas are classified into neoplasms of lymphoid precursors, which include lymphoblastic leukemias or lymphomas, and neoplasms of mature lymphoid cells. The latter include some 50 subtypes recognized in the World Health Organization classification system. Each subtype is associated with a set of genetic abnormalities, especially translocations involving antigen receptor genes, which may vary within a limited range (e.g. presence of other abnormalities, chromosomal breakpoints, variation in one of the translocation partners etc.). Occasionally, similar genetic abnormalities are present in different neoplasms (e.g., t(8;14) in BL and DLBCL). Gene and miRNA expression patterns are largely neoplasm-specific. Lymphomas appear to have a higher incidence in countries at a higher socioeconomic level, which increases with age, and are more common in men, although children are susceptible to a particular subset of lymphomas and some lymphomas have a particularly high incidence in certain geographical regions. Environmental factors known to be associated with a higher risk of lymphoma include chemicals (e.g., herbicides), solvents (e.g., benzene) and chronic infections (e.g., Helicobacter pylori). Diagnosis is normally made by histology and immunohistochemistry, but some lymphomas are associated with high levels of cytokines in serum and often, tumor-derived serum DNA. Other serum markers may correlate with prognosis – sometimes being a surrogate for tumor burden, such as lactate dehydrogenase, or are essential to management. Genetic polymorphisms may be associated with predisposition to lymphoma and response to therapy. There is broad scope for devices that may be particularly useful in resource-poor countries in helping to understand pathogenesis, speeding diagnosis, assessing tumor spread and predicting response and toxicity. Some could be useful in screening high risk patients, or patients at high risk for particular toxicities. The presence of specific plasma DNAs, genetic abnormalities or gene/miRNA expression patterns, polymorphisms, tumor markers and infectious agents are the most likely to produce valuable information via rapid, point-of-service, automated devices.

Stephen J. Meltzer

Gastrointestinal Malignancies

Hao Zhang, M.D., Department of Integrative Chinese and Western Medicine, Tumor Tissue Bank, and Oncological Research Lab, Cancer Hospital of Shantou University Medical College, Shantou, People's Republic of China and Cancer Research Center, Medical College of Shantou University, Shantou, People's Republic of China

and

Stephen J. Meltzer, M.D., Division of Gastroenterology, Departments of Medicine and Oncology and Sidney Kimmel Comprehensive Cancer Center, the Johns Hopkins University School of Medicine, Baltimore, Maryland.

International variations in cancer incidence and behavior are well-known. However, the molecular pathophysiologic basis of these differences is still poorly understood. Our laboratories in China and the United States are collaborating in studies of gastrointestinal (GI) tract tumorigenesis. We are studying genomic and epigenomic alterations in GI tumors and premalignant lesions from the two continents. For example, tyrosine phosphorylation, which is controlled by tyrosine kinases and protein-tyrosine phosphatases (PTPs), is important in the development of esophageal squamous cell carcinoma (ESCC). Compared with tyrosine kinases, our understanding of PTPs in ESCC is limited, and further knowledge could provide new therapeutic targets and diagnostic markers for this type of cancer. Protein tyrosine phosphatase receptor-type O (*PTPRO*), a new member of the PTP family, has been shown to function as a tumor suppressor in several forms of cancer. Inactivation of *PTPRO* by hypermethylation has been described in hematological malignancies and solid tumors. We therefore evaluated *PTPRO* hypermethylation as a potential epigenetic event and biomarker in ESCC.

Experimental Design: In 36 primary ESCC tissue specimens and matched peripheral plasma and buffy coat samples, as well as in ESCC-derived and immortalized normal esophageal cell lines, we determined the methylation status of *PTPRO* by performing methylation-specific PCR (MSP). Correlations with *PTPRO* methylation and clinicopathologic features were also examined.

Results: *PTPRO* hypermethylation was observed in 27 (75%) of 36 primary tumors and correlated significantly with depth of invasion (T-stage, $P = 0.013$). This high incidence of *PTPRO* methylation in primary tumors prompted us to further evaluate its clinical diagnostic value in peripheral blood. Among matched peripheral blood samples from ESCC patients, 13 (36.1%) of 36 had detectable methylated *PTPRO* in plasma, and 15 (41.7%) of 36 had it in the buffy coat. No methylated *PTPRO* was observed in normal peripheral blood samples from 10 healthy individuals. In addition, promoter methylation correlated with loss of *PTPRO* mRNA expression, and demethylation by 5-aza-dC treatment led to gene reactivation in *PTPRO*-methylated and -silenced ESCC cell lines.

Conclusions: Our findings suggest that hypermethylated *PTPRO* occurs frequently in ESCC. Its detection in the peripheral blood of ESCC patients, but not in that of normal controls, illustrates its potential clinical application as an epigenetic biomarker for noninvasive diagnosis and disease monitoring.

Aydogan Ozcan

Photonics based Telemedicine Technologies toward Smart Global Health Systems

Aydogan Ozcan, Ph.D.

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Today there are more than 4 billion cell-phone users in the world, and the majority of these cellphones are being used in the developing parts of the world. This massive volume of wireless phone communication brings an enormous cost-reduction to cellphones despite their sophisticated hardware and software capabilities. Quite importantly, most of these existing cellphones are also already equipped with advanced digital imaging and sensing platforms that can be utilized for various health monitoring applications. This impressive advancement is one of the central building blocks of the emerging fields of "Telemedicine" and "Wireless Health". The success of these fields will surely increase the quality of health care and reduce the insurance costs in developed countries like the United States, however, their most important and immediate impact will be to provide breakthrough technological solutions to various Global Health Problems including infectious diseases such as HIV, TB or malaria. Specifically, utilizing this advanced state of the art of the cell phone technology towards point-of-care diagnostics and/or microscopic imaging applications can offer numerous opportunities to improve health care especially in the developing world where medical facilities and infrastructure are extremely limited or even do not exist.

Centered on this vision, in this talk I will introduce fundamentally new imaging and detection architectures that can compensate in the digital domain for the lack of complexity of optical components by use of novel theories and numerical algorithms to address the immediate needs and requirements of Telemedicine for Global Health Problems. Specifically, I will present an on-chip cytometry and microscopy platform that utilizes cost-effective and compact components to enable digital recognition and 3D microscopic imaging of cells with sub-cellular resolution over a large field of view without the need for any lenses, bulky optical components or coherent sources such as lasers. This incoherent holographic imaging and diagnostic modality has orders of magnitude improved light collection efficiency and is robust to misalignments which eliminates potential imaging artifacts or the need for realignment, making it highly suitable for field use. Applications of this lensfree on-chip microscopy platform to high-throughput imaging and automated counting of whole blood cells, monitoring of HIV+ patients (through CD4 and CD8 T cell counting) and detection of waterborne parasites towards rapid screening of water quality will also be demonstrated. Further, I will discuss lensfree implementations of various other computational imaging modalities on the same platform such as pixel super-resolution imaging, lensfree on-chip tomography, holographic opto-fluidic microscopy/tomography. Finally, I will demonstrate lensfree on-chip imaging of fluorescently labeled cells over an ultra wide field of view of >8 cm^2, which could be especially important for rare cell analysis (e.g., detection of circulating tumor cells), as well as for high-throughput screening of DNA/protein micro-arrays.

Gregory Reaman

Cancer Detection and Diagnostics: Global Health Implications in Childhood Acute Lymphoblastic Leukemia (ALL)

Gregory Reaman, M.D.

Acute lymphoblastic leukemia(ALL) is the most common cancer in children and accounts for nearly 25% of all pediatric cancers. The peak age incidence of the disease is 2-6 years. Over the past 4 decades there have been dramatic improvements in outcome such that >80% of children are cured. Unfortunately, these advances in diagnosis and treatment are not accessible to significant numbers of children in resource-restricted parts of the world resulting in an unacceptable number of deaths in children. Many therapeutic discoveries including the use of multi-agent chemotherapy and the prophylactic treatment of pharmacological sanctuary sites have been responsible for the improved outcome. Most important, however, has been the recognition of the clinical and biologic heterogeneity of the disease which has very significantly impacted clinical treatment trials and subsequently standards of care for childhood ALL world-wide. Exploiting this heterogeneity has permitted the identification of clinical and biological prognostic factors of both host and disease origin which has resulted in the definition of risk groups. Perhaps in no other human cancer is treatment predicated on host clinical factors and biologic features of the disease to the extent which exists for children with ALL. Such a risk-adjusted therapy paradigm has become increasingly important as genomic investigations identify specific molecular abnormalities in the leukemic cells of patients with vastly different natural history which predict response to specific therapeutic interventions. As well, given the fact that the overwhelming majority of children survive, attempts to reduce therapy with the expectation of mitigating short and long term toxicity supports the use of risk-adjusted therapy approaches which continue to evolve as prognostic factors and risk groups are refined with newer and emerging technologies. The use of routine cytogenetics and the detection of sentinel chromosomal abnormalities using molecular and FISH have had a dramatic impact on redefining risk groups. The assessment of early response to therapy using more sensitive measures of minimal residual disease (MRD) detection has emerged as one of the most important prognostic factors, further expanding risk group definitions. Current approaches to MRD assessment using flow cytometric determination of leukemic cells detected by their unique immunophenotypic signatures has enabled sensitive detection methodology while decreasing the technical demands of previously required molecular techniques. Extending and enabling such technology to guide treatment decisions worldwide has the potential for enormous childhood public health impact by accurately selecting treatment interventions to selectively increase the intensity of therapy for patients thereby decreasing disease mortality. As well, decreasing intensity of therapy in select patients will decrease the incidence of short and long term toxicities and improve quality of survival.

Rebecca Richards-Kortum

Multi-Modal Optical Imaging to Improve Early Detection of Cancer in Low Resource Settings: Experience from China, India, Guatemala, and Botswana

Rebecca Richards-Kortum

Rice University

Medical imaging technologies have become increasingly important in the clinical management of cancer, and now play key roles in cancer screening, diagnosis, staging, and monitoring response to treatment. Standard imaging modalities such as MRI, PET, and CT require significant financial resources and infrastructure, which limits access to these modalities to those patients in high-resource settings. In contrast, optical imaging strategies, with the potential for reduced cost and enhanced portability, are emerging as additional tools to facilitate the early detection and diagnosis of cancer.

Optical imaging is a new technology which may provide a potential solution to the global need for affordable imaging tools to aid in the early detection and management of cancer. While healthcare providers have traditionally used optical tools such as endoscopes, colposcopes, and surgical microscopes in cancer management, a new generation of instruments is being developed which can detect not just reflected white light, but additional signals arising from cancer biomarkers, carried in the fluorescence, polarization, and narrowband reflectance of light. These systems are capable of examining tissue over a wide range of spatial scales, with widefield macroscopic imaging typically spanning several square-centimeters, and high-resolution *in vivo* microscopy techniques enabling cellular and subcellular features to be visualized. Optical instrumentation is relatively inexpensive, using mass-fabricated components developed by the telecommunications and consumer electronics industries. A second key factor is the recent emergence of multimodal optical imaging systems, simultaneously providing wide-field *and* high-resolution optical imaging, within cost-effective, portable, and even battery-powered formats.

This talk will present a vision for an expanding role for optical imaging in global cancer management, including screening, early detection at the point-of-care, biopsy guidance, and real-time histology. Multi-modal optical imaging – the combination of widefield and high resolution imaging - has the potential to aid in the detection and management of precancer and early cancer for traditionally underserved populations. Several recent widefield and high-resolution optical imaging technologies will be described, along with requirements for implementing such devices into lower-resource settings.

Lewis R. Roberts

Unmet Needs in Detection and Diagnostics for Hepatocellular Carcinoma: A Global Perspective

Lewis R. Roberts, MB ChB, PhD

Mayo Clinic College of Medicine

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third most frequent cause of cancer death worldwide, with an estimated 748,000 new cases and 695,000 deaths in 2008. The worldwide age-specific incidence ratio is 16.0 cases per 100,000 per year for men and 6.0 cases per 100,000 per year for women. Because of the low overall cure rate for hepatocellular cancer, the worldwide age specific mortality ratios are nearly identical to the incidence ratios at 14.6 deaths per 100,000 per year in men and 5.7 deaths per 100,000 per year in women. There are strong etiologic associations with chronic hepatitis B, chronic hepatitis, alcoholic cirrhosis, non-alcoholic fatty liver disease, other causes of chronic liver disease, and dietary aflatoxin exposure. Because these diseases and risk factors have distinct geographic distributions and different frequencies within different ethnic groups, there is also a preferential distribution of cases of HCC to certain geographic regions and specific at-risk populations. For example, approximately 55% of all HCC cases occur in Eastern Asia, including China,

Liver ultrasound, the current gold standard test for surveillance of HCC, is time consuming and requires a high degree of skill, even then, it only has a sensitivity of perhaps 60% in routine clinical practice. Alpha-fetoprotein, the serum test most often used in combination with liver ultrasound in surveillance for HCC, has a low sensitivity of 20-30% for detection of HCC in those patients with early stage disease who are most likely to be candidates for curative treatment. There is a significant unmet need for low cost, reliable tests for (i) identification of individuals with cirrhosis due to chronic viral hepatitis B or C or other causes of chronic liver disease who are at risk for development of HCC, (ii) early detection of HCC in at risk individuals, (iii) prediction of those patients who are most likely to benefit from specific therapies, for example the multikinase inhibitor, sorafenib, which is the only agent currently approved for treatment of advanced HCC, and (iv) assessment of overall prognosis of patients.

Jacqueline Sherris

Cancer Detection and Diagnostics Technologies for Global Health - Innovative responses to global health challenges

Jacqueline Sherris

PATH

PATH has had a long history of working in health technology development and introduction. Our work involves a deep engagement with key stakeholders health care providers, health systems, laboratory networks, commercial interests, and others. We also routinely engage, with the ultimate beneficiaries of a new health intervention, often women and their families and communities. Through this process we keep a strong focus on how a technology interacts with an overall health program and how it ultimately contributes to the overall health impact of that program. This lens has been crucial to our work on cervical cancer, which began by documenting the reality that the disease caused significant burden and suffering among the worlds poorest women, and the frustration of health providers who had nothing to offer them. In addition, our early work highlighted the challenges in scaling adequate quality Pap screening programs (and their resulting lack of health impact) which led us to collaborate on assessments of a number of alternative approaches for screening and treating women for precancerous lesions in low-resource settings. Our current work on the careHPV test is building evidence for how the test will function in the most difficult settings, what service delivery approaches and protocols will most effectively use the test, and what infrastructure and systems adaptations will be necessary to ensure that the test contributes to sustainable program impact. This presentation will discuss and reflect on this experience.

Samuel Sia

Microfluidics for global health diagnostics

Samuel Sia

Lab-on-a-chip (LOC) devices have a tremendous potential for improving the health of people in developing countries by providing immediate diagnosis in the field. The development of diagnostics for global health, however, presents unique and challenging design criteria. We will discuss our lab's current efforts, in conjunction with partners in industry, public health, and local governments, to develop new rapid diagnostic tests. Our tests span a variety of technologies, and target HIV, sexually transmitted diseases, and other infectious diseases.

Steven Soper

Polymer-Based Modular Microfluidic Point-of-Care System for Automated Genotyping

Steven A. Soper,[a,b,c] Mateusz L. Hupert,[a] Hong Wang,[a] Hui-wen Chen,[b] Donald Patterson,[a,e] Małgorzata A. Witek,[a,b] Proyag Datta,[d] Jost Gottert,[d] Michael C. Murphy,[a,c]

[a]Center for Bio-Modular Multi-Scale Systems (CBM^2), [b]Department of Chemistry, [c]Department of Mechanical Engineering, [d]Center for Advanced Microstructures and Devices (CAMD), [e]Louisiana State University, Baton Rouge, LA 70803, USA

Integration of the sample processing pipeline into a single system is of interest for point-of-care (POC) applications in the area of *in vitro* diagnostics, especially in 3rd world countries where resources are limited both from an infrastructure perspective and access to trained personnel. Microfluidics is a promising technology platform for POC applications as it can provide automated sample handling and reagent delivery as well as timely results with minimal operator intervention. We will discuss a microfluidic system for DNA analyses capable of detecting single nucleotide polymorphisms (SNPs) in a package incorporating all of the instrument peripherals that can accept a variety of clinical samples and search for the presence of mutations in genomic DNA that can provide important diagnostic information. Genomic DNA processing is carried out using a modular, polymer microfluidic, which consists of operational steps for cell sorting, cell lysis, solid-phase extraction of DNA, PCR amplification, discrimination reactions for identifying SNPs and readout using a low-density universal and programmable microarray. The microfluidic is manufactured as a 3-dimensional stack of 2 modules interfaced to a fluidic motherboard; a polycarbonate, PC, module used for solid-phase extraction and a poly(methyl methacrylate), PMMA, module used for detection of ligation products fitted with a monolithic laser coupling prism and air-embedded waveguide. The fluidic motherboard was made from PC and consisted of units for cell lysis, PCR, and a ligase detection reaction (LDR). As an application example, we will present results for the detection of point mutations in *BRCAI* genes. To further simplify the support peripherals, the laser-induced fluorescence detector could be eliminated by using LDR primers bearing gold nanoparticles; when silver stained, successful hybridization results could be read out using a digital camera. Results could be secured in <30 min compared to >12 h using conventional bench-top instrumentation. Due to the techniques used to fabricate the microfluidic system enabled by the substrate material choice, it can be manufactured and assembled in a high production mode at low-cost (<$10 per chip). In addition, modules can be added to the fluidic motherboard to expand the system's capabilities. For example, we have developed PMMA modules for selecting circulating tumor cells (CTCs), which will allow for the automated genotyping of selected CTCs in a variety of settings.

Edward L. Trimble

Diagnosis of Gynecologic Cancers

Edward L. Trimble, MD, MPH

Acting Director, Center for Global Health, NCI, NIH
Head, Gynecologic Cancer Therapeutics and Quality of Cancer Care Therapeutics, CIB, DCTD, NCI, NIH

The basic techniques used today for definitive diagnosis of invasive gynecologic cancers have not changed dramatically from those used 100 years ago. Diagnostic biopsies and surgical specimens are bathed in formalin for 8 to 24 hours, then graded concentrations of alcohol, followed by xylene. Next, the biopsies and portions of the surgical specimens are soaked in hot paraffin, which is then chilled and set. Using a microtome, thin sections of the tissue are cut and placed on glass slides. For the initial microscopic evaluation, the tissue is stained with hematoxylin and eosin. For additional accuracy, immunohistochemistry using monoclonal antibodies is performed on unstained slides. In situations when an immediate pathologic diagnosis is needed to guide surgery, tissue removed from a patient is frozen, cut on a microtome, placed on a glass slide and stained with hematoxylin and eosin. Overall, the process is cumbersome, resource-intensive, time-consuming, sensitive to the functionality of equipment and quality of reagents, and dependent on both skilled technicians for tissue processing and experienced anatomic pathologists for visual diagnosis.

Ovarian physiology and anatomy changes over a woman's lifespan, and, during her reproductive years, over her menstrual cycle. Benign ovarian cysts are common. Ultrasound and serum tumor markers are commonly used to define a 'risk-of-malignancy' index, which is used to guide clinical management. Asymptomatic ovarian masses at low risk of malignancy can be followed conservatively, without intervention. Symptomatic masses, and those at high risk of malignancy should lead to surgical intervention. During surgery, frozen section is generally used to confirm or refute an intra-operative diagnosis of cancer, as the extent of surgery is dependent on the presence or absence of cancer. After surgery, the definitive pathologic diagnosis is made using the techniques described above. Decisions as the use of chemotherapy given after surgery are made based on surgical findings and the final pathologic diagnosis.

In the late 1920's Professor George Papanicolaou determined that cervical epithelial cells could be easily obtained through scraping the cervix at the time of a speculum examination of the vagina. He observed that the morphology of these epithelial cells cells changes during a woman's menstrual cycle and that such sampling of cervical epithelial cells could identify precancerous changes prior to the development of invasive ovarian cancer. These observations led to the widespread use of the Pap smear to screen for precancerous lesions. After a traditional Pap smear has been made, the glass slide is batched with other Pap smear and reviewed for abnormal cellular changes by a cytotechnician, with secondary review by a cytopathologist. Abnormal findings are reported back to the clinician, who must recall the patient for colposcopy, an examination of the cervix under magnification, at which time additional biopsies of any suspicious areas are performed. These biopsies are then processed as described above, read by the pathologist, and the diagnosis reported back to the clinician, who must then determine the appropriate course of action. Conservative treatment of preinvasive cervical cancers is generally performed by excision with an electrocautery or a scalpel or freezing. Another treatment option is hysterectomy, which is generally reserved for cases when limited excision is not technically feasible. The very earliest stages of invasive cervical cancer can also be treated with excisional therapy. More advanced (but still early) cervical cancer is generally treated with hysterectomy. Locally advanced cervical cancer can be treated with primary chemoradiation or primary chemotherapy followed by surgery.

The diagnosis of endometrial cancer is generally presaged by abnormal uterine bleeding. In premenopausal women this may present as bleeding between menses or menses which are heavier than usual. In postmenopausal women this may present as bleeding or spotting or an increased vaginal discharge. Standard evaluation includes transvaginal ultrasound and endometrial biopsy. Ultrasound can determine the thickness of the endometrial lining. The most common cause of a thickened endometrial lining is hormonal imbalances, not endometrial cancer. Endometrial biopsy can generally be done in the outpatient setting with modest discomfort to the patient. Endometrial samples are processed as described above. Treatment of endometrial cancer generally begins with hysterectomy, followed by selective use of radiation and chemotherapy based on findings at hysterectomy and lymph node evaluation, if performed.

Shan X. Wang

Bench Top and Handheld Magneto-Nanosensor Platform for Multivariate In Vitro Diagnostics of Cancer

Shan X. Wang

Professor of Materials Science & Eng., and of Electrical Engineering, and by courtesy of Radiology, Stanford University

Reproducible and multiplex protein assays are greatly desired by cancer biologists as well as clinical oncologists to rapidly follow numerous proteins in clinical samples. We have now successfully applied magneto-nano biochips based on giant magnetoresistance (GMR) spin valve sensor arrays and magnetic nanoparticle labels (nanotags) to the detection of biological events in the form of multiplex protein assays (4-to 64-plex) with great speed (30 min. 2 hours), sensitivity (1 picogram/milliliter concentration levels or below), selectivity, and economy [1-3]. More recently, we achieved the first demonstration of a nanolabel-based technology capable of rapidly isolating cross-reactive antibody binding events in a highly multiplex manner. By combining magnetic nanotechnology with immunology, we have devised an easy to use and rapid auto-assembly assay which is ideal for high-density screens of aberrant protein binding events and for quantitative and multiplexed measurements of binding kinetics [4-5]. Furthermore, we have developed the auto-assembly assay for disease biomarker detection which obviates the need for washing steps and is run on a handheld sensing platform. By coupling magnetic nanotechnology with an array of magnetically responsive nanosensors, we demonstrate a rapid, multiplex immunoassay that eliminates the need for trained technicians to run molecular diagnostic tests. Furthermore, the platform is battery-powered and ultraportable, allowing the assay to be run anywhere in the world by any individual [6]. References: [1] Gaster RS, Hall DA, et al., Nature Medicine, 15, 1327-1332, 2009. [2] Osterfeld SJ, Yu H, et al., PNAS, 105, 20637-20640, 2008. [3] Hall DA, Gaster RS, et al., Biosensors and Bioelectron., 25, 2051-2057, 2010. [4] Gaster RS, Hall DA, Wang SX, Nano Letters, published online, DOI: 10.1021/nl1026056. [5] Gaster RS et al., Nature Nanotechnology, 6, 314-320, 2011. [6] Gaster RS, Hall DA, Wang SX, Lab on a Chip, 11 (5), 950 - 956, 2011.

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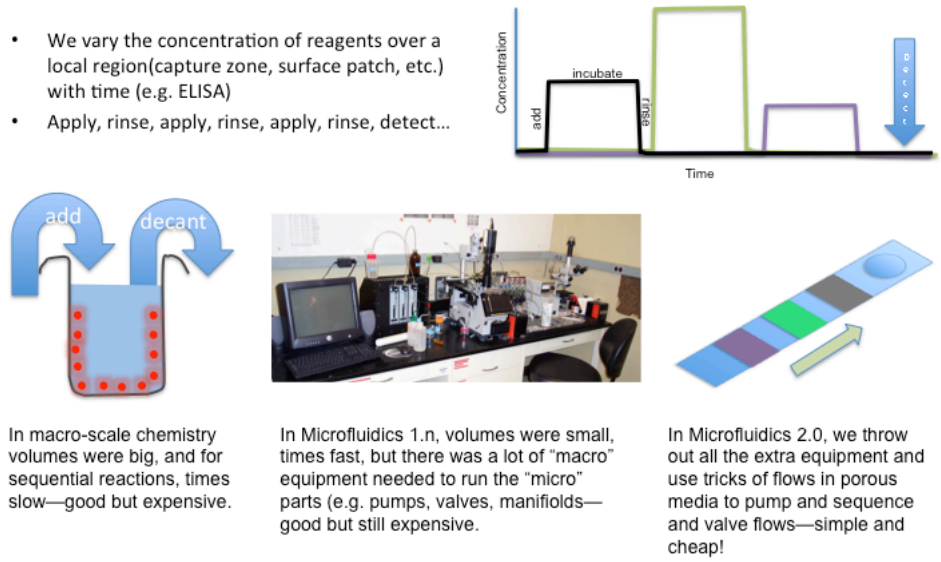
Paul Yager

Microfluidics 2.0: Dropping the Costs for Diagnostic Tests and Screening

Elain Fu, and Barry Lutz, and Paul Yager

Department of Bioengineering, University of Washington, Seattle, WA

When Microfluidics exploded in the 1990's, its main aim was to move from the discrete processing of fluids from container to container using manual pipettes or robots, to *integration* of the processes into monolithic devices. Microfluidics did that, and more, but at a cost---there were still pumps and pressure sources and valves needed to push the fluids around, and those things generally were big, expensive, and lived off the chip. Microfluidics 1.n systems are still, largely, in the big well-equipped labs.



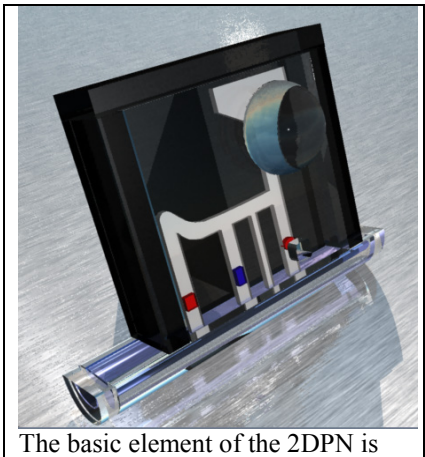
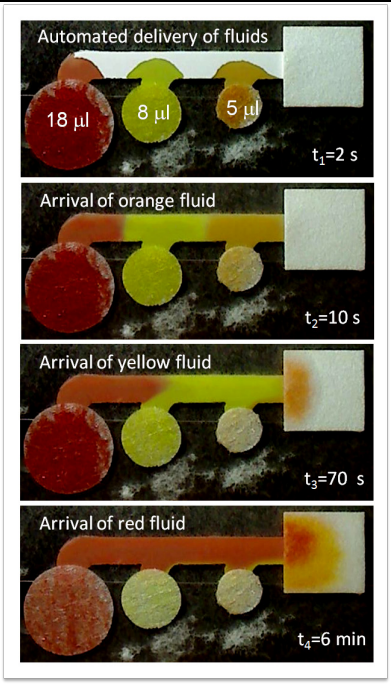
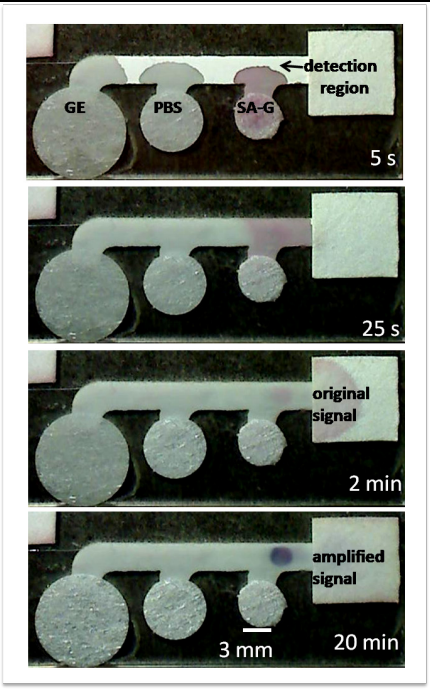
ELISA is still the best way to measure the concentrations of biomarkers. In ELISA, the approach is to cause sequential changes in reagent concentrations over a specific zone covered with capture molecules. The new capability in the two-dimensional paper networks used in Microfluidics 2.0 is the ability to sequence reagents at predictable concentrations for predictable times over multiple capture sites; this combines the best features of lateral flow tests with the best of "conventional" microfluidics.

By returning to what we've known for decades about moving fluids without pumps or valves in porous media, Microfluidics 2.0 offers us a chance to get the hoped-for advantages of microfluidics, but without the expense. Microfluidics 2.0 has the power to make sophisticated chemical and biochemical measurements much simpler, *and (a lot) cheaper*. By piggybacking on the revolution in information technologies, we can move the data generated anywhere in almost no time.

Technologies arising from Microfluidics 2.0 will:

- Allow quantitative measurement of small molecules, large proteins and nucleic acids at low concentrations in biological fluids rapidly and by anyone.
- Allow minimally trained personnel to perform chemical and biochemical analyses when and where they are needed.
- Reduce the cost of healthcare in the developed world by commoditizing a wide range of diagnostic tests (as has been done for blood glucose testing) to the point where early and frequent screening for disease is economical, voluntary and ubiquitous
- Bring sophisticated medical and agricultural diagnostics to low-resource settings—e.g., places in the developing world without the funds or infrastructure.

Some simple one-dimensional porous devices have been used in research tools and commercial products for decades (e.g., paper chromatography and lateral flow immunoassays). New and much more sophisticated devices and systems are now made possible by forming porous materials in complex shapes in 2 and 3 dimensions. Because fluid flow can be controlled precisely without the need for either positive displacement of pressure-driven pumps, the movement of the fluids (sample and all the reagents) is *programmed* by the structure of simple, inexpensive, single-use pieces of paper. Just add the sample, and perhaps some water, and the paper does the rest.

 The basic element of the 2DPN is the ability to sequence different chemicals by programming the size and shape of the paper network. Shown is a conceptual 2DPN activated by adding water to a single trough at the bottom.		
This 2DPN is a "monopapyric" paper circuit activated by addition of water; color changes in capture spots. There are two ways to activate the 2DPNs. This version is activated by wetting the bottom of the strips, which then suck up fluid and rehydrate multiple reagents; reagents are delivered sequentially as determined by the device geometry.	An alternative way to activate 2DPNs is to fold wetted pads onto an existing paper network (microfluidic origami). By filling the pads with wet reagents (or rehydrating dry reagents stored in each pad), the circuit is formed and the 2DPN delivers precise reagents to specific portions of the network near the wicking pad.	A simple demonstration of Increasing the sensitivity of the lateral flow immunoassay format by automating processing steps for chemical signal amplification in a simple 2DPN. Amplification by adding Au to captured Au nanoparticles (at right) results in a significantly darkened optical detection signal.

Characteristics of existing RDTs and the proposed multiplexed 2DPN rapid diagnostic tests

Characteristics	Conventional RDTs	2DPN rapid diagnostic
Sensitivity	Considered poor in many cases	Exceed existing RDTs by using chemical amplification of detection spots
Specificity	Adequate	Meet or exceed existing RDTs
Time	Less than 20 min	Less than 20 min
Training	Easy to use by untrained operators (CLIA waived to CLIA moderate)	Easy to use by untrained operators (goal: CLIA waived status)
Readout	Visible signal read by eye	Visible signal read by eye or quantified with a cell phone camera
Cost	Less than $1	Less than $1
Intended setting	Point-of-care	Point-of-care: physician's office or hospital ER
Sample conditioning	No	Yes—complex multistep processing possible
Multiplexable	Yes, but limited to ~4 capture lines	Highly
Adaptable	Yes	Yes, can be used generally for antigen detection (e.g. viral infections, bacterial infections, toxins)

Posters:

Author and Poster
Board Number List

Author List for
Technologies for Cancer Detection and Diagnostics (TTT), Global Health and Epidemiology of Cancer (GGG), and Molecular Analysis and Biomarker Research (MMM, BBB)

August 22, 2011, from 5:20 to 7:00 pm

Abaffy, Tatjana (BBB-94)
Detection of melanoma by non-invasive volatile metabolomic approach

Amarie, Dragos (TTT-1)
Advances towards Real-Time Single Cell Secretion Analysis using Microcavity Biosensors

Awdeh, Richard (TTT-2)
Optical Coherence Molecular Imaging Using Gold Nanorods in Living Mice Eyes

Baldwin, Dee (GGG-67)
Focus Group Findings in the Use of Technology in Reaching African American Women with Breast Cancer Messages

Belfield, Kevin (TTT-3)
Two-photon ex vivo tumor imaging

Berrier, Allison (BBB-95)
Carcinoma Matrix Controls Resistance to Cisplatin through Talin Regulation of NF-kB

Bubi, Tefo (TTT-4)
Multimodal Optical Imaging for the Detection of Cervical Neoplasia

Burke, Peter (TTT-5)
Assessment of mitochondrial membrane potential using an on-chip microelectrode in a microfluidic device

Camarero, Julio A. (MMM-81)
Cyclotides, an ultrastable protein scaffolds for targeting protein/protein interactions

Chang, Helena (MMM-82)
Proteomic-based biosignature for breast cancer detection—From tissue proteomic analysis to blood test development

Chen, Ray (TTT-6)
Photonic Crystal Microarray Nanoplatform for High-Throughput Highly Sensitive Detection and Identification of Cancers

Chung, Jae-Hyun (TTT-7)
Tip sensor platform for disease diagnosis and biomarker discovery

Cui, Juan (MMM-83)
An integrated approach for biomarker identification in gastric cancer

Datar, Ram (TTT-8)
Innovative Membrane Microfilter Device for Tumor Cell Capture and Analysis in Resource-Limited Settings

DeVoe, Don (TTT-9)
Zero-Power Disposable Microfluidic Assays for Global Health

Dharmawardhane, Suranganie (BBB-97)
Noncoding RNA signature for triple negative breast cancer

Dickerson, Samuel (TTT-10)
Isolating Particles on Lab-on-Chip Platforms using Time-Multiplexed Dielectrophoresis

Dickman, Kate (BBB-96)
Aristolochic Acid Nephropathy: An Environmental and Iatrogenic Disease

Dwyer, Chris (TTT-11)
Engineering Sensor-Actuator Pharmaceuticals by DNA Self-assembly

Efird, Jimmy (BBB-98)
Effective design and statistical analysis of cancer detection and diagnosis protocols

Fan, Rong (TTT-12)
Single Cell Microtechnology and Systems Oncology

Frustino, Jennifer (MMM-84)
Autofluorescence-Guided Diagnostics for Lesions of the Oropharynx

Georgakoudi, Irene (TTT-13)
Confocal backscattering-based detection of leukemic cells in flowing blood samples

Gilad, Assaf (TTT-14)
MRI of Gene Expression

Globus, Tatiana (TTT-15)
Highly Resolved Sub-Terahertz Spectroscopic Technique and Sensor Combined with Microfluidics for Molecular and Cells Diagnostics

Gorfinkel, Vera (TTT-16)
Novel Instrumentation Complex for Molecular Diagnostics and Personalized Medicine

Gouma, Perena (TTT-17)
Portable and handheld cancer detecting breathanalyzers

Gracias, David (TTT-18)
Thermo-Biochemically Responsive, Tetherless Microsurgical Tools

Guerrero-Preston, Rafael (BBB-99)
Methylation portraits from the front-lines: Towards a world-wide network for cancer early detection and diagnosis research in low-income countries

Hanas, Jay (TTT-19)
Early Detection of Cancer Using Electrospray Mass Spectrometry

Hashsham, Syed (TTT-20)
Gene-Z™: A Simple and Low-Cost Hand-held Platform for Measurement of microRNAs and Other Genetic Markers of Cancer

Hassan, Ahmed (TTT-21)
The Diffusion-Drift Algorithm for Modeling the Biopotential Signals of Breast Tumors

Heyduk, Tomasz (BBB-100)
Comprehensive strategy for autoantibody-based analysis of cancer

Holland, Lisa (TTT-22)
Microscale sequencing of glycans relevant to cancer

Hu, Tony (TTT-23)
Biomarker Discovery and Disease Staging on Proteomic Nanochips

Hughes, William (TTT-24)
Synthetic DNA Reactions for Low-cost Diagnosis of Cancer

Isaac, Rita (GGG-68)
Translating evidence into practice in low resource settings: An experience of establishing a model Cancer Cervix screening programme in rural Tamilnadu, India

Jin, Moonsoo (MMM-85)
Inflamed Leukocyte-mimetic Nanoparticles for Molecular Imaging of Inflammation and tumor microenvironment

Kachnowski, Stan (TTT-25)
Mobile Solutions for Cancer Management, Medication Adherence and Health-related Behavior Change

Kast, Rachel (TTT-26)
Development of Fractal and Electrode Components for Organotypic Culture in a Novel Three-Dimensional Bioreactor System

Kiesel, Peter (TTT-27)
Opto-fluidic Detection System Enabling Sophisticated Point-of-care Diagnostics

Kuhn, Peter (TTT-28)
Liquid Biopsy in Solid Tumors

Kumar, Challa (TTT-29)
Attomolar Detection of a Cancer Biomarker Protein in Serum by Surface Plasmon Resonance Using Superparamagnetic Particle Labels

Lelievre, Sophie (TTT-32)
A global endeavor towards primary prevention with the international breast cancer and nutrition (IBCN) project: Novel bioengineering-based detection and diagnostic initiatives

Li, Lin (TTT-30)
A Combination of Multiple Scattered Light Spectroscopy/Polarized Light Spectroscopy Technology for Rapid Noninvasive Diagnosis of Skin Cancer

Lin, Yuehe (TTT-31)
Biofunctionalized Nanoparticles and Graphene for Cell Imaging and Cancer Diagnostics

Lisovicz, Nedra (GGG-69)
Support for a community-based breast and cervical cancer prevention and control program in Dar es Salaam, Tanzania

Liu, Yaling (TTT-33)
Efficient Circulating Tumor Cell Capturing in Microfluidic Devices

Lo, Justin (TTT-34)
Development of a compact, cost-effective spectroscopic imaging device for tissue absorption and scattering

Lo, ShihChung (TTT-35)
Statistically Significantly Improved Nodule Detection in Rib Suppressed Chest Radiography:

Loehr, Jordann (GGG-70)
HPV and Cervical Cancer Screening, Prevention, and Treatment in Post-Crisis Reproductive Health Care Packages: A Needed Intervention for Refugee and Displaced Women

Luk, Yan-Yeung (MMM-86)
Squaramide-Based RGD Mimics A Potent Cell Adhesion Ligand for Functionalizing Multivalent Agents and Organic Microcapsules.

MacAulay, Calum (TTT-36)
In silico Optical Physical Model (iPOM) of the cervical epithelium: a tool to facilitate the implementation of new optical technologies in low-resource countries

Merkler, David (MMM-87)
Biotinylated, Photoactivable Adenosine Analogs as Proteomic Profiling Tools

Mirica, Katherine (TTT-37)
Density-Based Analysis with Magnetic Levitation

Naughton, Michael (TTT-38)
Capacitive Nanosensor for Multiplexed Molecular Detection of Biomarkers

Nieva, Jorge (TTT-39)
High Definition Imaging of Circulating Tumor Cells and Associated Cellular Events in non-Small Cell Lung Cancer Patients; a longitudinal analysis

Nittayananta, Wipawee (GGG-71)
Effects of Long-Term Use of Antiretroviral Therapy on the Prevalence of Oral Epstein-Barr Virus

Odeniyi, Folasade (GGG-72)
Cervical Cancer in Nigeria: The Case for Multidisciplinary Action

Paiva, Marcos (GGG-73)
Improvement of palliative laser thermal therapy by identifying biomodulators that will impact outcomes

Panchapakesan, Balaji (BBB-101)
Electrical Properties of Cells on NanoStructured Thin Film Surfaces: An Approach towards Detection of Rare Tumor Cells

Paszat, Lawrence (GGG-74)
Biomarkers of gastric cancer and its precursors: potential to reduce gastric cancer mortality around the world

Phelan, Catherine (GGG-75)
BRCA1 and BRCA2 mutations in Mexican women with breast cancer

Pierce, Mark (TTT-40)
Low-cost microendoscopy for in situ identification of cervical neoplasia

Pommier, SuEllen (GGG-76)
A New Method for Testing the Estrogen Receptor Status of Breast Cancers in Low Resource Countries

Protano, Marion-Anna (TTT-41)
Low-cost microendoscopy for the diagnosis of esophageal squamous cell neoplasia in northern China: an evaluation of interobserver agreement and accuracy

Puskas, Judit (MMM-88)
New Method for the Exclusive?—Conjugation of Folic Acid

Puzey, Kenneth (BBB-102)
IR Spectroscopy for automated low cost molecular diagnosis of cancer

Qin, Lidong (TTT-42)
Integrated Microfluidic devices for Assays of Cancer Cell Migration, Invasion, and Protein Expression

Rasal, Rajashri (GGG-77)
Knowledge and attitudes of HIV-infected and HIV-uninfected women regarding HPV and cervical cancer

Reinhard, Bjoern (TTT-43)
Plasmon Coupling in Cancer Biomarker Detection and Quantification

Reinhold, Vernon (MMM-89)
Coupling Quantitative HPLC Profiling with In-depth MSn Disassembly for Comprehensive Structural Characterization of Neutral and Sialylated N-linked glycans

Rusling, James (TTT-44)
Microfluidic amperometric arrays for panels of cancer biomarkers

Sanchez, Gloria (BBB-103)
Evaluation of strategies for optimal clinical management of women with atypical squamous cells of undetermined significance (ASCUS): Design and Pilot phase.

Schwartz, Elena (BBB-104)
New Panel of Predictive Biomarkers for Metastatic Colorectal Cancer Patients Stratification

Schweizer, Johannes (TTT-45)
Development of the AV Avantage HPV E6 Test for Detection of Cervical Pre-Cancer and Cancer in Low-Resource Settings

Sequin, Emily (TTT-51)
Eddy Current Measurement: A Novel Tool for Detecting Cancer

Shah, Anjali (GGG-78)
Prostate Cancer Incidence and Survival Analysis and Trends

Shin, Hye-Won (BBB-105)
Gas Biomarkers from Leukocytes: Non-Invasive Disease Detection of Hematopoietic Malignancy

Shrotriya, Pranav (TTT-52)
Aptamer Functionalized Microcantilever Based Sensing Approach for Small Molecules

Smith, Edward (BBB-106)
A Non-Invasive Method of Brain Tumor Detection: Urinary Biomarkers Predict Brain Tumor Presence and Response to Therapy

Sokolov, Igor (TTT-53)
Atomic force microscopy as a prospective tool in the detection of cancer cells

Su, Ming (TTT-46)
Multiplexed reconfigurable biomarker detection using solid-liquid phase change nanoparticles

Sun, Ya-Ping (TTT-54)
Toward Fluorescence Imaging of Breast Cancers with Newly Developed Carbon Dots

Tankhilevich, Boris (TTT-55)
The Terahertz Magnon Photon Laser Imaging System (TERMAPLIS)

Tchente Nguefack, Charlotte (GGG-79)
Epidemiology and surgical management of breast cancer in Douala General Hospital

Troyer, Dean (MMM-90)
Metabolomics and Histology on the Exact Same Tissue Sample: Preservation by Extraction and Fixation

Vargis, Elizabeth (TTT-47)
Detecting Cervical Dysplasia in Minority Populations using Raman Spectroscopy

Vilozny, Boaz (TTT-56)
Label-free Biomarker Detection with Quartz Nanopipettes

Vriesendorp, Huib (GGG-80)
The Doctors Dilemma Anno 2011

Wang, Guiren (TTT-57)
Isolation and enrichment of cancer cells

Wang, Quanzeng (TTT-48)
Optical property measurement in layered tissues: Discrimination between normal and dysplastic mucosa phantoms

Wang, Silun (BBB-107)
Amide proton transfer MRI signal as a novel imaging biomarker for assessing radiation necrosis in the rat brain

Wang, Tza Huei (Jeff) (TTT-58)
Quantum Dots and Single Molecule Detection Technologies for Highly Sensitive Detection of Circulating DNA Cancer Markers in Clinical Samples

Weisz, Judith (MMM-91)
Fourier-transform Infrared Microspectroscopy Identifies Chronic Oxidative-Stress Associated Molecular Changes in Mammary Epithelium of Young Women: Insight into Early Latent Stage of Breast Carcinogenesis

Won, Chang (TTT-49)
Malignant Tumor Detecting System using Tactile Images

Xin, Hao (TTT-59)
Microwave Induced Thermal Acoustic Imaging and Spectroscopy for Potential Breast Cancer Detection

Xu, Shoujun (TTT-60)
A New FIRMS Technique for Molecule-Specific Magnetic Imaging of Cells

Yamal, Jose-Miguel (TTT-50)
Accuracy of optical spectroscopy for the detection of cervical intraepithelial neoplasia and the role of probe placement

Yeung, Anthony (BBB-108)
Mucin 5B may be a Specific Indicator of Mucinous Pancreatic Cysts

Yoon, Euisik (TTT-61)
Single Cell Assay Chips for Cancer Drug Screening and Pairwise Cell-to-Cell Interactions

Yoon, Seongkyu (TTT-62)
Chemometrics based image processing and delineation for the intraoperative mapping of nonmelanoma skin cancer

Yu, Bing (TTT-63)
A smart fiber optic sensor for detection of oral and cervical cancer in developing world

Yuan, Baohong (TTT-64)
Development of an ultrasound-mediated fluorescence imaging technique for cancer detection

Zhang, John X.J. (TTT-65)
Immunomagnetic Nano-Screening Chip for Circulating Tumor Cells Detection in Blood

Zheng, Yun-Ling (BBB-109)
Telomere length variation in normal epithelial cells adjacent to tumor: a potential biomarker for breast cancer local recurrence

Zhou, Jinyuan (BBB-110)
Novel Molecular MRI Approach for Assessment of Brain Tumors and Radiation Response

Zhou, Yang (MMM-92)
Imaging Bread Cancer Metastasis by u-SPECT/CT with Tc-99m-3P-RGD2

Zhu, Liang (TTT-66)
Magnetic nanoparticle hyperthermia: In vivo heating experiments using implanted prostatic tumors and microCT imagings of nanoparticle distribution

Zong, Wei-Xing (MMM-93)
Elevated expression of squamous cell carcinoma antigen (SCCA) is associated with human breast carcinoma

Author List for
Technologies and Prototypes Demonstration (TD)

August 22, 2011, from 5:20 to 7:00 pm

Andres, Christine (TD-A), University of Michigan
SWNT-Paper Sensor

Balsam, Joshua (TD-B), FDA
Low-Cost Optical Biosensing for Global Health

Bau, Haim H. (TD-C), University of Pennsylvania
Molecular Diagnostics at the Point of Testing

Chen, Ellen (TD-D), ABS, Inc.
Powering the Medical Devices in the Global Health Setting

Chung, Jae-Hyun (TD-E), University of Washington
MEMS/Nanotechnology: Tip sensor platform for disease diagnosis and biomarker discovery

Garra, Brian (TD-F), FDA
Ultrasound and Portable X-Ray Technology for Global Health

Godayarty, Anuradha (TD-G), Florida International University
Hand-Held Optical Imaging Technology

Hashsham, Syed (TD-H), Michigan State University
Gene-Z: A Rapid & Inexpensive Gene Analyzer for High-End Diagnostic Applications

Iqbal, Samir (TD-I), University of Texas at Arlington
Circulating Tumor Cells in Microfluidic Devices for Global Health

Jung, Woonggyu (TD-J), University of Illinois
Handheld optical imaging scanner for advanced point of care diagnostics

Khine, Micelle (TD-K), University of California, Irvine
Shrink-Film Microfluidics for Inexpensive and Rapid Devices

Mancuso, Matthew (TD-L), Cornell University
Detection of Kaposi's Sarcoma causing Herpes Virus using Lab-on-a-Syringe Technology

Markovic, Nenad (TD-M), Global Acad. Women's Health
Low Cost Medical Devices Combined with Telemedicine Reduce Health Disparities between Developed and Developing Countries

Ozcan, Aydogan (TD-N), UCLA
Photonics-based Telemedicine Technologies toward Smart Global Health Systems

Peck, Roger (TD-O), PATH
Technologies to Expand Cervical Cancer Screening Coverage in Low-Resource Settings

Phillips, Scott (TD-P), Pennsylvania State University
Paper-Based microfluidic devices that contain fluidic batteries and fluidic timers for conducting quantitative colorimetric assays

Pleic, Maja (TD-Q), Harvard University
Book Presentation

Qin, Lidong (TD-R), Cornell University
Integrated Microfluidic devices for Assays of Cancer Cell Migration, Invasion, and Protein Expression

Richards-Kortum, Rebecca (TD-S), Rice University
Demonstration of High Resolution Microendoscope for Cancer Screening in Low-Resource Settings

Schweizer, Johannes (TD-T), Arbor Vita Corp.
Lateral-flow test for detection of cervical pre-cancer and cancer in low-resource settings

Sia, Samuel (TD-U), Columbia University
Microfluidics for global health diagnostics

Soper, Steven (TD-V), Louisiana State University
Polymer-Based Modular Microfluidic Point-of-Care System for Automated Genotyping

Tang, Cha-Mei (TD-W), Creatv MicroTech
Rapid and Efficient Isolation of Circulating Tumor Cells Using High Porosity Precision Microfilters

Wang, Guiren (TD-X), University of South Carolina
Microfluidics for Isolation and Enrichment of Cancer Cells

Wang, Tza Huei (Jeff) (TD-Y), Johns Hopkins University
Quantum dots and Microfluidics for Rapid Screening of Cell-Free DNA Biomarkers

Wang, Shan X. (TD-Z), Stanford University
Bench Top and Handheld Magneto-Nanosensor Platform for Multivariate In Vitro Diagnostics of Cancer

Williams, Anthony (TD-AA), University of Miami
Innovative Membrane Microfilter Device for Tumor Cell Capture and Analysis in Resource-Limited Settings

Xiang, Yu (TD-BB), University of Illinois
Using portable glucose meters for low-cost quantification of various non-glucose analytes related to health and environment

Yager, Paul (TD-CC), University of Washington
Microfluidics 2.0: Dropping the Costs for Diagnostic Tests and Screening

Yu, Bing (TD-DD), Duke University
A smart fiber optic sensor for detection of oral and cervical cancer in developing world

Poster Abstracts:

Technologies for Cancer Detection and Diagnostics

TTT-1

Advances towards Real-Time Single Cell Secretion Analysis using Microcavity Biosensors – Dragos Amarie

Dragos Amarie[1], Aaron Dy[1], Alin Cosmanescu[1], Gens, John Scott[1], Dwayne Stupack[2], and James A. Glazier[1]

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In living tissues, cells secrete a wide variety of molecules into their surroundings. Secretion patterns change as cells grow, differentiate, interact or become damaged and diseased. Diffusible molecules play key roles in the embryonic development, immune system, wound healing, tissue homeostasis, and diseases such as cancer.

The CCN1 expression in breast cancer promotes tumorigenicity, metastasis, antihormone, and chemoresistance. It is critical in vertebrate gastrulation, vasculogenesis, placentation, as well as chodrogenesis. The precise cellular secretion and temporal pattern are unknown. Although scientists suppress gene expression using siRNA or shRNA technology, it remains unclear how well the Cyr61gene is suppressed, particularly when the levels of mRNA transcribed can vary widely. Existing technologies provide no temporal information or can only be interpreted grossly, yet this information is crucial to the ability to accurately interpret the myriad of experiments performed in biological laboratories every day. While most biosensors are used to detect and analyze biochemical reagents in fast, economical assays for environmental monitoring, medical diagnostics, food safety and security, very few have been successful at monitoring protein secretion at the single-cell level. Currently, no technique can simultaneously: (1)-measure diffusible extracellular molecules quantitatively, (2)-quickly measure changes in concentration over a period of minutes, (3)-be sensitive enough to quantify physiologically relevant concentrations of molecules produced by a single cell, (4)-sort and recover the selected cells, (5)-use cells without genetic modification or external input of chemical labels, (6)-allow quick redesign and extension to high-throughput, and (7)-be inexpensive enough for wide use in research and technology.

We developed a new technology, the microcavity surface-plasmon-resonance biosensor (MSPRS), to study the binding kinetics of unlabeled molecules based on these principles. They are one micron diameter and integrate well with microfluidics. Preliminary data for using MSPRS technology for studying single-cell secretion of CCN1 will be presented.

We acknowledge support from NIH/NIGMS grant R01-GM76692, NAKFI and the Office of the Vice President for Research of Indiana University.

TTT-2

Optical Coherence Molecular Imaging Using Gold Nanorods in Living Mice Eyes – Richard Awdeh

Richard M. Awdeh[1], Adam de la Zerda[2A], Victor L. Perez[1], Marco Rugerri[1], Sanjiv Gambhir[2B]

[1]Ophthalmology, Bascom Palmer Eye Institute, Miami, FL; [A]Molecular Imaging Program, [B]Bioengineering & Materials Science and Engineering, [2]Stanford University, Palo Alto, CA.

Optical Coherence Tomography (OCT) is a powerful imaging modality used to visualize ocular structures with high spatial resolution. The contrast in an OCT image is mainly due to the tissue optical scattering properties. Hence, an OCT image primarily visualizes structures. For OCT to reach its full potential in imaging physiological and molecular processes, exogenous contrast agents may be useful. Such contrast agent should produce a strong OCT signal, beyond the background tissue OCT signal. Here we demonstrate for the first time that gold nanorods (GNRs) can be used as contrast agents for OCT in living subjects. GNRs possess a tunable and strong optical absorbance due to their plasmon resonance in the NIR region. The GNRs used here are 13 nm in diameter and 45 nm in length, resulting in an absorbance peak at 780 nm. A low dosage of 50 nM gold nanorods that was injected into living mice corneas produced significant OCT contrast, 6-fold higher than that of control mice injected with saline. We experimentally estimated the sensitivity of GNR in living mice corneas to be 370 pM, which with their small size, makes GNR a highly promising imaging agent for OCT.

This project is funded by the NIH/ NEI R21 EY020940 (RMA). We would like to thank NCI CCNE U54 CA119367 (SSG), NCI ICMIC P50 CA114747 (SSG), the Bio-X Graduate Student Fellowship (AD), and the DoD Breast Cancer Research Program (AD) for supporting this work. We thank Jianhua Wang for the use of his OCT laboratory in order to acquire OCT images.

TTT-3

Two-photon ex vivo tumor imaging – Kevin Belfield

Kevin D. Belfield[1]*, Ciceron O. Yanez[1], Alma R. Morales[1], Carolina Andrade[1], Xuhua Wang[1], Takeo Urakami[2], Masanobu Komatsu[2]

[1]Department of Chemistry, University of Central Florida, Orlando, FL; [2]Sanford-Burnham Institute for Medical Research at Lake Nona, Orlando, FL

Two-photon fluorescence microscopy (2PFM) offers several advantages, such as deeper tissue penetration along with more confined excitation and emission that leads to an increase in imaging resolution. Although biomedical applications of two-photon fluorescence microscopy (2PFM) are steadily increasing, the technique still suffers from the lack of efficient, photostable two-photon absorbing fluorescent probes that possess high target specificity. In order to be truly useful for such applications, it is necessary to have not only an imaging component that undergoes two-photon absorption (2PA) at wavelengths longer than 700 nm, but also a vector that targets the fluorescent probe selectively to a particular tissue, cell, organelle, receptor, or protein. We describe approaches to 2PFM imaging that targets important biomarkers, including proteins that are expressed in tumors and the targeting of vasculature around the tumors rather than tumors themselves. In this work, we describe the preparation and the use of novel, efficient two-photon absorbing (2PA) fluorescent probes that target the vascular endothelial growth factor 2 (VEGFR-2), folate receptors, and integrin proteins. Comprehensive linear and nonlinear photophysical and biological characterization of the new probes will be presented along with 2PFM imaging.

National Institutes of Health (1 R15 EB008858-01 to K.D.B. and 1 R01 CA125255 to M.K.), the U. S. Civilian Research and Development Foundation (UKB2-2923-KV-07), the Ministry of Education and Science of Ukraine (grant M/49-2008), the National Science Foundation (CHE-0840431 and CHE-0832622), and Florida Department of Health, Bankhead-Coley Cancer Research Program (10BD-11 to T.U).

TTT-4

Multimodal Optical Imaging for the Detection of Cervical Neoplasia – Tefo Bubi

Tefo Bubi[1], Mark Pierce[1], Doreen Ramogola-Masire[2,3], Rebecca Richards-Kortum[1]

[1]Department of Bioengineering, Rice University, Houston, USA; [2]School of Medicine, University of Botswana, Gaborone, Botswana; [3]Botswana-UPENN Partneship, Gaborone, Botswana

Despite being the most preventable type of cancer, cervical cancer is the third leading cause of cancer death among women worldwide. Over 80% of cervical cancer incidence and mortality occurs in developing countries where screening programs for early detection are either inadequate or unavailable. Developing countries often lack infrastructure necessary to implement current screening tools. Due to their low cost and ease of interpretation at the point-of-care, optical imaging technologies may serve as an appropriate solution for cervical cancer screening in low resource settings. The objective of this research is to explore a combination of wide-field and high-resolution optical imaging of the cervix to aid in the early detection of cervical neoplasia in low-resource settings. We have developed a portable wide-field optical imaging system which uses filtered LED illumination and a compact CCD camera to acquire macroscopic cross-polarized, narrowband reflectance and fluorescence images of the cervix to highlight areas suspicious for neoplasia. We have also developed a high-resolution optical imaging system which can be used to interrogate suspicious areas with higher spatial resolution. Both the widefield and high resolution imaging systems can be used with fluorescent contrast agents to enhance image contrast and highlight changes in biomarkers of neoplasia. We report results of a pilot study in Botswana using proflavine, a fluorescent dye which stains nuclei, as a contrast agent. Preliminary studies demonstrate the ability of the imaging systems to provide enhanced visualization of several parameters known to be involved in the onset and progression of cancer; cross-polarized imaging eliminated superficial reflections, narrowband imaging provided increased contrast of neo- vasculature, and fluorescence imaging enables the uptake and distribution of the nuclear-binding topical contrast agent, proflavine. Optimally combining wide-field and high-resolution imaging of the cervix may aid in the early detection of cervical neoplasia in low-resource settings.

National Institute of Biomedical Imaging and Bioengineering, NIH.

TTT-5

Assessment of mitochondrial membrane potential using an on-chip microelectrode in a microfluidic device – Peter Burke

Tae-Sun Lim, [1]* Antonio Davil[1,2], Douglas C. Wallace[2], and Peter Burke[1]

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The mitochondrial membrane potential is used to generate and regulate energy in living systems, driving the conversion of ADP to ATP, regulating ion homeostasis, and controlling apoptosis, all central to human health and disease. Therefore, there is a need for tools to study its regulation in a controlled environment for potential clinical and scientific applications. For this aim, an on-chip tetraphenylphosphonium (TPP+) selective microelectrode sensor was constructed in a microfluidic environment. The concentration of isolated mitochondria (Heb7A) used in a membrane potential measurement was 0.3 ng mL□1, four orders of magnitude smaller than the concentration used in conventional assays (3 mg mL□1). In addition, the volume of the chamber (85 mL) is 2 orders of magnitude smaller than traditional experiments. As a demonstration, changes in the membrane potential are clearly measured in response to a barrage of well-known substrates and inhibitors of the electron transport chain. This general approach, which to date has not been demonstrated for study of mitochondrial function and bio-energetics in generally, can be instrumental in advancing the field of mitochondrial research and clinical applications by allowing high throughput studies of the regulation, dynamics, and statistical properties of the mitochondrial membrane potential in response to inhibitors and inducers of apoptosis in a controlled (microfluidic) chemical environment.

This work was supported in part by the following grants awarded to D.C.W.: NIH-AG24373, NS21328, AG13154, DK73691, CIRM Comprehensive Grant RC1-00353, and a Doris Duke Clinical Interface Grant 2005057. P.B. acknowledges support of this work from NIH National Cancer Institute Grant1R21CA143351-01. Antonio Davila is supported by the National Science Foundation Lifechips Integrative Graduate Education and Research Traineeship 0549479.

TTT-6

Photonic Crystal Microarray Nanoplatform for High-Throughput Highly Sensitive Detection and Identification of Cancers – Ray Chen

Ray Chen[1,2], Swapnajit Chakravarty[2], Wei-Cheng Lai[1]

[1]Department of Electrical and Computer Engineering, University of Texas, Austin; [2]Omega Optics, Austin, TX

We demonstrate a high throughput label-free microarray based on photonic crystal microcavity devices. The devices show the ability to simultaneously test probe antigen-target antibody binding events at multiple spots with a single measurement. Preliminary results have shown the capability to test probe antigen-target antibody binding events at 72 spots with a single measurement. The photonic crystal microcavity, which defines the sensor spot, has a dimension of 1 micron by 0.5 micron. We have demonstrated high sensitivity of our devices compared to commercially available label-free biosensors at very low concentrations approximately 100pico-molar of the probe protein with projected sensitivity down to 10pico-molar. The high sensitivity is enabled by high microcavity quality-factors Q~3430 in bio ambient that enable detection of small changes in the individual microcavity resonant frequency, in addition to the intrinsic property of photonic crystals being highly sensitive to small changes in the refractive index of the ambient. Specific advantages with respect to ring resonator based, surface-plasmon based and grating based label-free bio-sensing platforms will be discussed. The device will enable the development of a portable, diagnostic device suitable for highly parallel, high throughput label-free biomolecule detection in multiple areas such as in the identification of cancers and allergies, in new biomarker discovery, with high sensitivity and specificity. The device is fabricated with standard lithography steps employed in a CMOS foundry which ensures fabrication in an extremely cost-effective way.

National Cancer Institute, SBIR Contract #: HHSN261201000085C

TTT-7

Tip sensor platform for disease diagnosis and biomarker discovery – Jae-Hyun Chung

Jae-Hyun Chung[1], Kyong-Hoon Lee[2]

[1]Mechanical Engineering at University of Washington, Seattle, WA; [2]NanoFacture Inc, Bellevue, WA

The presented technology combines mechanical and electrohydrodynamic concentration, affinity binding, and capillary action in novel fashion, with unprecedented results. The major innovation is in the concentration of target biomarkers onto a microscale- or nanoscale tip for florescence detection. The presented system concentrates particles to a microtip by using mechanical flow, an electric field, binding affinity, and capillary action. We envision this tip enrichment system as a fundamental tool to provide solutions for early cancer diagnostics and biomarker discovery, in particular, of global health. Due to the simple device action without centrifugation steps, the device will allow the detection of circulating tumor cells, DNA, and other biomarkers with low cost. The major functions of this system are (1) high throughput enrichment and transfer of cells, nucleic acids, proteins, and other biomarkers (2) multiplexing platforms for fluorescence microscopy, electron microscopy, mass spectrometry, etc. and (4) biobanking and preservation of targets.

TTT-8

Innovative Membrane Microfilter Device for Tumor Cell Capture and Analysis in Resource-Limited Settings – Ram Datar

Anthony Williams[1], Ram Datar[1], Yu-Chong Tai[2], and Richard Cote[1]

[1]Department of Pathology, University of Miami-Miller School of Medicine, Miami, Florida; [2]Department of Electrical Engineering, California Institute of Technology, Pasadena, California

Metastasis, the most important determinant in the management of cancer, accounts for >90% of patient mortality. Clinical guidelines of post-treatment patient surveillance often require frequent and long-term follow up accompanied with expensive, invasive and sometimes inefficient techniques. Detecting the rare circulating tumor cells (CTC) has emerged as a means of providing a more efficient and non-invasive approach to detect early evidence of metastasis and enable therapeutic monitoring. While numerous technologies (most immunoaffinity-based) have been developed in recent years to isolate CTC, difficulties with sensitivity, specificity, efficiency, and high costs of these assays have limited their clinical translation. We developed a novel membrane microfilter device to enrich and capture CTC directly from patient blood. This platform has a superior sensitivity and efficiency as seen in published head-to-head comparison with the CellSearch® platform. Owing to its open-format, beyond enumeration, the microfilter also allows for CTC characterization by techniques such as multi-marker immunofluorescence, FISH, PCR and CGH. Our cell-size-based approach, in contrast to immunoaffinity-based platforms, is 'antigen expression-agnostic'; allowing analysis of even tumor types lacking target antigens. The microfilter also has a potential to capture and analyze tumor cells from other body fluids such as urine, plural effusions, cerebrospinal fluid and ascites. Portability, low production cost, easy uniformity and reproducibility in manufacture, and rapid sample processing are unique characteristics of the microfilter device. For rural and underserved communities where blood samples must otherwise be sent to distant, centralized laboratories for analysis, the microfilter can be used as a point-of-care alternative platform, and has the transformative potential to provide a cheaper and easier alternative with significantly rapid turn-around time for CTC isolation. With the ability to perform multiple, repeated sample analyses to detect recurrent disease early and enable therapeutic monitoring, the microfilter can revolutionize the patient management, and improve health care delivery globally.

TTT-9

Zero-Power Disposable Microfluidic Assays for Global Health – Don DeVoe

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A practical, low cost, and zero-power thermoplastic microfluidic platform designed for use in resource-constrained environments is described in this work. The platform enables rapid and sensitive multiplexed protein biomarker assays by integrating a suite of novel microfluidic capabilities in a manually-operated system, requiring no external instrumentation for chip operation while achieving low per-patient screening costs. The system integrates functionalities including on-chip collection and purification of whole blood from a finger prick inlet, manual bistable pumps for actuating the flow of sample and reagents, and reliable microfabricated burst valves enabling long-term storage of lyophilized protein probes and other reagents within the chip. Arrays of microporous detection zones fabricated from polymer monoliths are integrated within selected regions of the chip, enabling sensitive and rapid assay times by leveraging the small diffusive length scales, high surface area, and low hydrodynamic resistance inherent to the discrete volumetric detection elements. Furthermore, a new assay readout format based on layer-by-layer nanoparticle dendridic amplification is being developed to enable quantitative colorimetric detection using a cell phone camera, enabling the chips to operate with no external power source and eliminating the need for complex instrumentation for optical or electrical readout.

TTT-10

Isolating Particles on Lab-on-Chip Platforms using Time-Multiplexed Dielectrophoresis – Samuel Dickerson

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In this work, we propose a new technique for separation and isolation of biological particles. The foundation of our method is dielectrophoresis, a technique where electric fields can be used to differentiate particles based on their inherent electrical properties rather than markers. These electrical properties reflect differences not just in particle mass and volume, as current methods exploit, but also capture subtle variations in the internal composition of the particle. Using a novel time-multiplexed combination of dielectrophoresis methods over very dense electrode arrays, we can create strong electric fields with a high degree of spatial resolution. Thus particles with variations in composition can be made to experience different amounts of force, forces in opposite directions, or no force at all simply by applying particular field frequencies and phases in particular regions of the electrode array. By creating these spatially distributed configurations of dielectrophoresis fields, we can generate differential forces that enable us to isolate and hold in position specific particle types that would otherwise be indistinguishable using other methods. The proposed methodology has the potential to serve as the basis for a new class of point-of-care, portable diagnostic devices by allowing researchers to sort and assay particles of interest based on their structure and composition without the use of expensive and destructive biochemical labeling techniques.

TTT-11

Engineering Sensor-Actuator Pharmaceuticals by DNA Self-assembly – Chris Dwyer

Chris Dwyer[1]

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Despite major advances in personalized medicine enabled by rapid, low-cost genetic sequencing, and the promise of biochip/MEMS for high-throughput diagnostics, routine blood and tissue analysis remains impractical to bring to the clinical bedside. Existing approaches where blood or tissue samples are drawn or biopsied and brought to an analysis lab are effective but do not offer more optimal, real-time feedback between current physiological conditions and potential treatments, e.g., similar to a pulse oximeter for blood oxygen content. This project investigates methods and theory from nanoscience and computer engineering to develop new diagnostic and pharmaceutical tools for clinical use. The approach is to apply recent advances in DNA nanotechnology and label-free optical sensing to build the principles and techniques for a suite of pharmacological sensor + actuator compounds which can: (i) transduce circulating and tissue-bound markers into easily detectable optical signals, and (ii) respond to external stimuli by altering the morphology of the compound, in vivo. The concept is to integrate computational functionality, through DNA self-assembly, and biologicallyrelevant diagnostic capabilities (e.g., through antigen sensitive receptors) into injectable compounds which facilitate real-time and otherwise complex or time-consuming blood and tissue assays. Leveraging decades of institutional experience with dye-oximeter blood gas techniques, this project uses common bedside technologies to communicate with and control sophisticated blood borne nanoscale structures. Beyond diagnostics, this work may also enable real-time interactions between circulating nanostructures and health monitors to implement tightly coupled feedback loops, e.g., between a drug metabolite and its pro-drug. The project overview and recent demonstrations of label-free, optical sensing of various biomolecules on integrated DNA nanostructures will be presented.

TTT-12

Single Cell Microtechnology and Systems Oncology – Rong Fan

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Tumors are so heterogeneous at the single cell level as reflected by the hierarchical complexity of tumor microenvironment. To identify all the cellular components, including both tumor and infiltrating immune cells, and delineate the associated cell-cell communication network that dictates tumor initiation, progression and metastasis, we developed a sub-nanoliter immumoassay chip that can analyze single cell proteomics signature and potentially reveal the inter-cellular signaling network associated with cancer and the immune system. It was realized by integrating two advanced technologies microfluidic single cell handling and ultra-high density protein array. This device was first dteste for highly multiplexed profiling of secreted proteins including tumor-immune signaling molecules from several hundred single cells or small cell colonies in parallel. We measured a dozen proteins secreted from human monocytic leukemia cells and observed profound cellular heterogeneity with all functional phenotypes quantitatively identified. Correlation analysis further indicates the existence of an intercellular cytokine network in which TNFa-induced secondary signaling cascades further increased polyfunctional cellular diversity. This platform is further extended to analyze the heterogeneous cellular composition of a solid tumor tissue derived from a patient with glioblastoma multiforme. It was also exploited to evaluate polyfunctionality of tumor antigen-specific T cells from melanoma patients being treated with adoptive T cell transfer immunotherapy. In the end, this nanobiotechnology platform will be applied to probing complex tumor microenvironment from small amounts of clinical specimens, e.g. skinny needle biopsies, and thus provide a powerful means for patient stratification based upon molecular signatures and signaling network.

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TTT-13

Confocal backscattering-based detection of leukemic cells in flowing blood samples – Irene Georgakoudi

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The prognostic value of assessing minimal residual disease (MRD) in leukemia has been established with advancements in flow cytometry and PCR. Nonetheless, these techniques are limited by high equipment costs, complex and costly cell processing and the need for highly trained personnel. Here, we demonstrate the potential of exploiting differences in the relative intensities of backscattered light at three wavelengths to detect the presence of leukemic cells in samples containing varying mixtures of white blood cells (WBCs) and leukemic cells flowing through microfluidic channels. Using 405, 488 and 633 nm illumination, we identify distinct light scattering intensity distributions for Nalm-6 leukemic cells, normal mononuclear (PBMC) and polymorphonuclear (PMN) white blood cells and red blood cells. We exploit these differences to develop cell classification algorithms, whose performance is evaluated based on simultaneous acquisition of light scattering and fluorescence flow cytometry data. When this algorithm is used prospectively for the analysis of samples consisting of mixtures of PBMCs and leukemic cells, we achieve an average specificity and sensitivity of leukemic cell detection of 99.6%, and 45.2%, respectively. When we consider samples that include leukemic cells along with PMNs and PBMCs, which can be acquired using a simple red blood cell lysis step following venipuncture, the specificity and sensitivity of the approach decreases to 91.6% and 39.5%, respectively. Based on the performance of these algorithms, we estimate that 42 or 71 μL of blood would be adequate to confirm the presence of leukemia at an 80% power level in samples containing 0.01% leukemia to either PBMCs or PBMCs and PMNs, respectively. Therefore, light scattering based flow cytometry in a microfluidic platform could provide a low cost, highly portable, minimally invasive approach for detection and monitoring of leukemic patients. This could offer significant improvements especially for pediatric patients and for patients in developing countries.

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TTT-14

MRI of Gene Expression – Assaf Gilad

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Chemical exchange saturation transfer (CEST) based MRI is a highly promising avenue for studying genetic events. In this approach, different protons can be tagged at different resonance frequencies. This enables the detection of multiple targets simultaneously. Our research is focused on developing imaging probes for two well characterized anti-cancer therapeutic genes which are also used as reporter genes: cytosine deaminase (CDase) and Herpes simplex virus 1-thymidine kinase (HSV1-tk). Our findings suggest that two substrates of the enzyme CDase, cytosine and anti-cancer pro-drug, 5-fluorocytosine (5FC), can be detected using specific saturation radiofrequency (2ppm and 2.4ppm from water respectively). Indeed, after deamination to uracil and 5-fluorouracil respectively, by recombinant CDase, the CEST contrast disappears. In addition, expression of the enzyme in three different cell lines, manifested in different expression levels, was in good agreement with CDase activity measured with CEST MRI. The enzymes HSV1-tk phosphorylates thymidine and has been evaluated in the clinic for cancer gene therapy using pro-drugs such as ganciclovir as well as for PET imaging using imaging probes (e.g. [124I]-FIAU and [18F]FHBG). Thymidine has NH (imino) protons that provide a CEST contrast following radiofrequency saturation at 5ppm from water. By chemical modifications we increased the imino protons pKa value, which consequently reduced, its exchange rate resulting in improved CEST MRI contrast compared to thymidine. Furthermore, the modified substrate showed higher specificity toward HSV1-tk over mammalian TK, thus making it a more selective imaging probe. Real-time monitoring of the activity of therapeutic genes by CEST MRI could guide personalized medicine. Thus, this new approach is the first steps en route to developing new technologies for cancer diagnosis, prognosis and treatment.

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TTT-15

Highly Resolved Sub-Terahertz Spectroscopic Technique and Sensor Combined with Microfluidics for Molecular and Cells Diagnostics – Tatiana Globus

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Terahertz (THz) vibrational spectroscopy is an emerging technique for characterization of biological and organic materials. THz spectroscopy for identification and characterization is based on the specificity of the spectroscopic pattern, showing absorption of THz radiation at characteristic resonance frequencies. Here we show results on the development, implementation, and testing of a new optical, frequency-domain, resonant, and selective, spectroscopic sensor system with imaging capability, operating at room temperature in the sub-THz spectral region. The sensor prototype is combined with a microfluidic sample device that enhances coupling of radiation with the sample material. The prototype provides spectral resolution better than 0.035 cm-1, an order of magnitude improved detection sensitivity compared with a commercial laboratory instrument requiring detector operation at 1.7 K, and spatial resolution below the diffraction limit. For this spectrometer, highly resolved transmission (absorption) spectra with strong narrow spectral lines were obtained from as little as 10-20 ng of biological macromolecules (DNA and proteins). Experimental results for the protein thioredoxin are confirmed by comparison with molecular dynamic (MD) simulations. Since genetic components and proteins contribute significantly to the signature of cells, specific cell types can be differentiated, and these results are presented. This method promises high discriminative capability not only between species, but between different strains, such as pathogens and non-pathogens of the same specie. Previously we conducted research on the application of THz spectroscopy to discriminate between different forms of cancer cells. The improved instrumentation and microfluidic device presented here has the potential to now provide a fast and effective modality to improve detection of human cancers in excised samples. Combined with traditional methods of molecular and tissue diagnostics, sub-THz Vibrational Spectroscopy promises to add optical, quantitative genetic information to the diagnostic analysis thus increasing the accuracy of fast cancer detection.

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TTT-16

Novel Instrumentation Complex for Molecular Diagnostics and Personalized Medicine – Vera Gorfinkel

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The instrumentation complex GenometricaLab performs a variety of molecular-diagnostic tests based on ultra fast and highly accurate detection of multi-color fluorescence from labeled objects (DNA molecules, color beads, quantum dots, etc.). GenometricaLab consists of a novel single photon spectrometer and capillary sample analyzer. In the sample analyzer the labeled objects are moved through the capillary by either air pressure or electric field. The fluorescence emitted by the labeled objects is received by the spectrometer in 32 spectral channels in the range of 450nm-750nm. Due to a highly advanced analog/digital circuitry, the spectrometer has a unique performance: linearity up to 108 photon/s/channel, data acquisition rate up to 106 frames/s, and data recording speed up to 32MB/s during many hours. The GenometricaLab system has been successfully used for detection of very low abundant samples (less than 100 fluorophores) in bead detection and electrophoresis modes. In the CE mode GenometricaLab can perform fragment analysis with up to 8 different fluorescent labels and do DNA sequencing (readlength up to 800bp). As a bead reader, the system can register up to 100,000 bead/s and based on combinations of 6 types of quantum dots it can recognize up to 100,000 different color combinations with 96% accuracy.

TTT-17

Portable and handheld cancer detecting breathanalyzers – Perena Gouma

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The detection and monitoring of gases in exhaled human breath up to date has been limited by the lack of appropriate materials and technology that could rapidly and selectively identify the presence and monitor the concentration of trace levels of specific analytes-biomarkers. This abstract refers to a new, inexpensive, non-invasive breathanalyzer technology that has the potential to revolutionize personalized medicine. Our breath analyzer technology detects specific gaseous biomarkers that the medical literature has associated with certain medical conditions, from asthma to lung cancer. It has the potential to recognize even a few molecules of each specific biomarker in a single breath exhaled. It only takes milliseconds to give out the reading of the gas concentration. The principle of its operation is selective resistive chemosensing. Selective sensor arrays suitable for real-time discrimination and monitoring of bio-chemical metabolites that signal diseases are described. For example, based on the selective oxidation catalysis of hydrocarbons, discrimination between biomarkers such as ethane and isoprene may be readily achieved. One example is the use of vanadium phosphorus oxide (VPO) nanoparticles as catalytic dopants for the selective detection of ethane by rutile oxide structures. The design and use of a handheld breath analyzer for gas detection in exhaled human breath are described. Its prospective use by underprivileged populations with limited healthcare options is as exciting as its potential to provide an early warning for silent killer diseases such as lung cancer.

Perena Gouma received grants DMR0304169 and DMR0224642 from the National Science Foundation.

TTT-18

Thermo-Biochemically Responsive, Tetherless Microsurgical Tools – David Gracias

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Surgery has evolved from invasive to minimally invasive procedures with the ultimate frontier being elusive thus far; non-invasive surgery. We describe a step in this direction by the creation and in vivo deployment of sub-millimeter scale tools such as grippers that close or open autonomously in response to body temperature or chemicals such as enzymes. These microgrippers have been used to perform both in vitro (biopsy) and in vivo (tissue sampling) surgical tasks. The highlights of this approach are that the tools can be fabricated and actuated en masse, are small enough to pass through catheters and hard to reach places in the body, can be created with sharp tips and are strong enough for tissue excision, can be magnetically guided from afar and do not need any wires or tethers.

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TTT-19

Early Detection of Cancer Using Electrospray Mass Spectrometry – Jay Hanas

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We are having success distinguishing sera of early-stage (I/II) cancer patients (pancreatic, lung, ovarian) from healthy control individuals. These studies are based on the hypothesis that tissues and organs are shedding/secreting biomolecules into the peripheral blood due to homeostatic reactions including defense/stress responses, and that these biomolecule profiles will change with physiological state including disease states and their progression. Detection of early-stage tumor products and imprints in sera is also a possibility. These early-stage cancer test sensitivities are presently in the 80% range which could be useful for screening high risk individuals. As many more sera samples are analyzed and also as the overall methodology and technology is improved, these test sensitivities are likely to increase. We are using a novel paradigm involving identification of significant sera mass peak differences between cancer patients and control individuals using electrospray ionization (ESI) mass spectrometry (MS) and serum profiling to accomplish these goals. ESI-MS not only has the ability to resolve hundreds and even thousands of serum biomolecules (which is likely necessary for detection of early cancer stage progression) but also has the ability to identify these molecules. Such identifications can yield new biomarkers and cancer mechanisms/paradigms and also provide targets for novel therapeutic approaches. We believe this electrospray mass spectrometry approach using small sera volumes can be developed into a useful and relatively inexpensive early-stage cancer detection methodology and platform.

Oklahoma Tobacco Research Center, Southwest Program for Pancreatic Cancer, Oklahoma Center for the Advancement of Science and Technology

TD-20

Gene-Z™: A Simple and Low-Cost Hand-held Platform for Measurement of microRNAs and Other Genetic Markers of Cancer – Syed Hashsham

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Currently available genetic analysis platforms are powerful but they are expensive and too complicated for use by non-experts. We have developed a small and low cost device, called the Gene-Z™, which is an isothermal genetic analysis platform operated by an iPod Touch or Google's Android tablets. Features of the device include: i) simple microfluidic chips consisting of 64-1536 wells of 1 μl each, ii) quantitative isothermal amplification of DNA, RNA, and microRNAs, iii) 10-30 min assay time, and iv) potential for GPS and networking of multiple devices. Unique elements of the molecular approach include: i) simple modifications of microRNAs to be able to amplify and detect using loop mediate isothermal amplification, ii) use of highly specific genetic signatures extracted from a large number of allelic sequences, and iii) use of SYTO 82 dye to track isothermal amplification (LAMP) using simple photodiodes. It is envisioned that the cost of the device will be less than $1,000 with disposable chips ranging from $2-$20 based on the density and application. Because microRNAs are small, their detection and quantification is difficult. A novel approach employing extension of the microRNAs followed by specific amplification by LAMP was developed and validated under laboratory conditions. We have been able to consistently amplify 10^4-10^5 copies within 10 min and 10-100 copies in less than 50 min. Amplification of DNA markers and mutation detection on the Gene-Z™ platform can be accomplished directly. Future research includes the validation of the approach developed for microRNAs and other cancer markers using clinical specimens to establish specificity, sensitivity, and other assay parameters. These assays for cancer markers using Gene-Z™ will allow rapid and low cost detection of established cancer markers under field conditions.

TTT-21

The Diffusion-Drift Algorithm for Modeling the Biopotential Signals of Breast Tumors – Ahmed Hassan

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Breast cancer is the most common cancer diagnosed and the second leading cause of cancer related deaths for women in the U.S. Nevertheless, existing breast cancer screening methods suffer from substantial limitations which have fueled a great interest in developing new detection techniques. Biopotential signals produced by breast tumors have the potential to act as a safe, non-invasive and low cost screening modality. Biopotential signals arise during cell division due to electrophysiological activities such as variations in membrane potential and ion channels expressions. This poster presents a novel multiscale model which links the electrophysiological activities at the cell level and the macroscopic biopotential signals recorded at the surface of the breast. The basis of the model is the diffusion-drift algorithm which involves the numerical solution of the coupled and highly non-linear Poisson, Nernst-Planck and Continuity equations. The simulation of hundreds of cells using the model is computationally extensive. Therefore, different parallelization techniques to speed up the model using High Performance Computing (HPC) resources will be discussed. Finally, the model results for various tumors will be presented and the effect of different tumor shapes and division stages on the generated biopotential signals analyzed. The model results show that tumor morphology has a significant impact on both the spatial and temporal patterns of the generated biopotentials. The current clinical standard of the biopotential detection of breast cancer places one electrode directly above the center of the tumor. However, the model results show that the point above the center of the tumor might not be the point of maximum biopotential. Therefore, employing a uniform fine array of sensors on the surface of the breast could yield better diagnostic results. The model results can have important clinical implications when using the biopotential signals for breast cancer detection.

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TTT-22

Microscale sequencing of glycans relevant to cancer – Lisa Holland

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Phospholipid preparations are a unique additive for capillary electrophoresis analyses of glycans. This self-assembled nanomaterial supports enzyme reactions in capillary, facilitates separation of glycans with subtle differences in structure, and steers fluids through intersecting microfluidic channels. At temperatures below 24 C, aqueous phospholipid preparations have viscosity similar to water, but become gel-like at 29 C. As a thermally reversible pseudo-gel, this additive can be easily introduced into a capillary channel at 24 C and then transformed into a highly viscous media with an increase in temperature of only 5C. Glycans labeled with 1-aminopyrene-3,6,8-trisulfonic acid are separated with efficiencies as high as 640,000 theoretical plates and detection limits of 15 femotmolar. The media has been integrated with proteins that interact with glycans, including lectins and enzymes. The use of in-capillary enzymatic cleavage of terminal glycan residues with exoglycosidases offers a number of advantages over bench top enzymatic sequencing, including reduced consumption of analyte, as well as enzyme. The benefit of phospholipid additives for glycan separations is demonstrated and the method is exploited to probe glycan structure.

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TTT-23

Biomarker Discovery and Disease Staging on Proteomic Nanochips – Tony Hu

Jia Fan, Jason Sakamoto, Adaikkalam Vellaichamy, Mauro Ferrari, Ye Hu

The Methodist Hospital Research Institute

Many studies have investigated how circulating low molecular weight (LMW) proteome can reflect ongoing pathological conditions in patients. We have previously reported the synthesis of mesoporous silica (MPS) chips of tunable pore size, texture, and structure for the selective capture of LMW proteins and peptides from complex bodily fluid. With the assistance of mass spectrometry, the MPS chip technology we developed for this study provides unprecedented performance in: 1) biomolecular analyses, 2) addressing the fundamental bottlenecks that have limited the use of blood proteomics and peptidomics for the early detection of cancer, and 3) for the monitoring of therapeutic efficiency. In parallel with this work, we developed new nanochips with unique post-synthetic functionalization on pore surface, some of which are illustrated as the following figure. These include MPS chips doped with zirconium or gallium metal ions for selectively isolating and enriching phosphorylated proteins and peptides, which is especially important for analyzing cell and tissue lysates. Nanohips functionalized with boronic acid for the enrichment of glycosolated proteins are also under development. The new chips increase the affinity for proteins that have undergone phosphorylation or glycosylation, key post-translational modifications that, if over-expressed, may indicate oncogenic behavior. These aberrantly modified biomarkers are present in the serum proteome at low concentrations that require accordingly low detection thresholds for early biomarker identification. We have shown that the nanochip-based technology can be used to identify subtle changes in protein expression patterns. To validate this technology and the MPS chips under development for the capture and identification of human breast cancer biomarkers, we have initiated a prospective study using paired fresh blood and bone marrow specimens collected from biopsy-proven stage I-III breast cancer patients.

NIH, NCI, Alliance of NanoHealth

TTT-24

Synthetic DNA Reactions for Low-cost Diagnosis of Cancer – William Hughes

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From an engineering perspective, DNA is to chemical reaction networks as silicon is to transistors. As modular components, DNA reaction networks can be interconnected to perform complex calculations chemically much the same way that transistors can be combined to perform calculations electronically. By harnessing this computational power, DNA reaction networks can be engineered to detect cancer-specific miRNAs in human blood, amplify the signal, analyze the amplified signal, and generate an observable output for diagnosis. To offer flexibility and scalability, our approach uses modular reaction networks that consist of a translator, cross-catalytic amplifier, and reporter. The translator module accepts a target miRNA as an input signal and outputs a specific DNA sequence, which then acts as the input into the amplifier module. The multiplied output of the amplifier module drives the reporter module. The reporter module generates a colorimetric change in vitro based on relative miRNA concentrations signifying a positive/negative diagnosis, analogous to the results of a disposable pregnancy test. As miRNAs are linked to over 258 diseases, this concept is broadly applicable to human health. In this study, we report initial progress in the development of a DNA reaction network engineered to amplify cancer-related miRNAs. Subcomponents of the DNA network were tested individually, and their operation in serum, as well as a mixture of serum with sodium dodecyl sulfate, is demonstrated. Simulations of the full cross-catalytic network indicate successful operation. As a model system, we tested the operation of an autocatalytic network in human serum and mouse serum. The network was found to operate successfully with the addition of sodium dodecyl sulfate to prevent nuclease degradation. Finally as a simple test system, a synthetic DNA machine, switchable between three mechanical states by DNA fuel, was successfully operated in 100% human serum and blood.

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TTT-25

Mobile Solutions for Cancer Management, Medication Adherence and Health-related Behavior Change – Stan Kachnowski

Stan Kachnowski

Healthcare Innovation and Technology Lab, Mary W. Lasker Building

Over the last ten years, cellular telephones have become a ubiquitous feature of the American landscape. More recently, with the drop in consumer prices, smart phones have enjoyed increasing popularity. Public health practitioners have been quick to take advantage of these trends, sparking a mobile health revolution that targets nearly every disease. Cellular devices have proven especially invaluable to clinical management, medication adherence, and health-related behavior change for chronic conditions. Yet mobile health interventions that address these three issues for cancer are relatively scarce. This article proposes to fill this gap by highlighting how mobile phones can be used to manage symptom burden, improve adherence to complicated medication regimens and promote healthy lifestyle choices for at-risk patients. Our research, past and present, suggests this approach is likely to lead to improved health outcomes because cellular phones facilitate health communication that is more tailored, interactive, frequent, and consequently more effective. This poster presents a review of existing mobile health interventions and highlights promising new areas where such transfers of current cellular technologies should be deployed.

TTT-26

Development of Fractal and Electrode Components for Organotypic Culture in a Novel Three-Dimensional Bioreactor System – Rachel Kast

Heather Hanni[1], Rachel Kast[2], Tara Twomey[3], Michelle Brusatori[2,3], Gregory Auner[1,2,3]

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Current research in modeling mammary gland and breast cancer formation has evolved in the development of three-dimensional (3D) culture models. We propose a novel 3D cell culture model with tree-like fractal scaffolds to induce 3D growth by inhibiting the 2D spatial growth and providing gaps between groups of cells. The use of fractal scaffolds will bridge the gap between in-vivo response and current cell based modeling and allow a comprehensive in-vitro study of the role of metabolic stress in tumor growth and therapeutic responsiveness. Fabrication of freestanding fractal scaffolds made of SU8 and coated in gold was achieved with high reproducibly using photolithography. Fractal scaffolds were examined in a seven-day study to determine cell proliferation and viability. Results showed the middle-density fractals induced 3D growth and increased proliferation against a positive control. Futhermore, we present multifunctional electrodes for stimulation of cells during cancer formation. Pt-80%/ Ir-20% wires with a 200μm diameter were micro-patterned using an excimer laser and fluence ranging from 3.4 J/cm2 to 2.5J/cm2 with a constant 500 pulses and a repetition rate of 10 Hz. Micro patterning with a fluence of 3.4 J/cm2 allowed for a separation of platinum and iridium, which increased the charge storage capacity and decreased the impedance. This preliminary data provides us an insight in developing a novel, three-dimensional bioreactor with cell stimulating electrodes. Future work will include stacking of fractal scaffolds with microfluidic channels, and incorporation of glycoaminoglycans (GAGs) to enhance three-dimensional growth towards mammary and tumor formation. Development of a functional bioreactor will allow for advanced diagnostic measurements of tumor cells grown in an organotypic environment.

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TTT-27

Opto-fluidic Detection System Enabling Sophisticated Point-of-care Diagnostics – Peter Kiesel

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Most biomedical tests are performed at large clinical laboratories because compact, robust, and inexpensive instruments for point-of-care (POC) testing are simply not available. Yet there is a need for POC testing. Optofluidic systems for fluorescence detection of bio-particles offer high performance, but they cannot meet POC specifications. We have demonstrated, prototyped, and benchmarked against commercial systems a new optical detection approach that delivers high signal-to-noise discrimination without complex optics or bulky excitation sources. It therefore enables a truly compact, low-cost, high-performance microfluidic-based instrument that can be used for diagnostics on whole blood and for other complex fluids. The enabling technique is termed spatially modulated emission and generates a time-dependent signal as a continuously fluorescing bio-particle traverses a predefined pattern for optical transmission. Correlating the detected signal with the known pattern achieves high discrimination of the particle signal from background noise. In conventional flow cytometry, the size of the excitation area is restricted approximately to the size of the particle. Our method allows a large excitation area to increase the total flux of fluorescence light that originates from a particle. Despite the large excitation area, the mask pattern enables a high spatial resolution which permits independent detection and characterization of near-coincident particles, with a separation (in the flow direction) that can approach the dimension of individual particles. In addition, the concept is intrinsically tolerant to background fluorescence originating from fluorescent components in solution, fluorescing components of the chamber and contaminants on the surface. The detection technique has been evaluated with measurements of absolute CD4+ and percentage CD4 T-lymphocytes counts in human blood. More recent experiments demonstrate that the platform can address a large variety of diagnostic needs including multiplexed bead-based assays (ELISA on-the-flow) and identification and enumeration of pathogens (e.g., Giardia, Cryptosporidium and E. Coli) in fluids.

This work is partially supported by a grant from the NIH and ARO.

TTT-28

Liquid Biopsy in Solid Tumors – Peter Kuhn

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The liquid biopsy is a unique opportunity to investigate and manage solid tumors at the single patient level over the entire course of the disease. The NCI Scripps Physics Oncology Center has developed standardized protocols for the liquid biopsy and is using the to address basic research questions of intravasation, travel patterns, survival and extravasation of circulting tumor cells in patients.

This work is supported by the National Cancer Institute's Physics Oncology Initiative

TTT-29

Attomolar Detection of a Cancer Biomarker Protein in Serum by Surface Plasmon Resonance Using Superparamagnetic Particle Labels – Challa Kumar

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Methods to measure protein biomarkers with ultralow detection limit (DL) and high sensitivity promise to provide valuable tools for early diagnosis of diseases such as cancer, and for monitoring therapy and post-surgical recurrence. Surface plasmon resonance (SPR) utilizing nanoparticle antibody labels for signal amplification in immunoassays is an emerging approach for detecting proteins in biomedical samples. Herein, we show for the first time that clustering of superparamagnetic labels on SPR sensor surfaces leads to unprecedented sensitivity and ultralow DL for protein biomarkers in serum. Specifically, antibody bioconjugates on 1 mm diameter superparamagnetic particles (MP) used for off-line antigen capture enabled SPR detection of cancer biomarker prostate specific antigen (PSA) in serum at an ultralow DL of 10 fg per mL□ (ca. 300 aM). This approach opens new doors for accurate diagnostics based on new protein biomarkers at low concentrations.

This work was financially supported by the NIEHS/NIH (U.S. PHS grant ES013557 to J.F.R.) and by the NSF (grant DMR-0604815/1005609 to C.V.K.).We thank Aparna Iyer for SEM measurements. S.K. and V.M. contributed equally to this work.

TTT-30

A Combination of Multiple Scattered Light Spectroscopy/Polarized Light Spectroscopy Technology for Rapid Noninvasive Diagnosis of Skin Cancer – Lin Li

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An estimated 160,000 people each year develop melanoma, the most dangerous form of skin cancer, and about 48,000 melanoma related deaths occur worldwide yearly according to the recent World Health Organization (WHO) report. As such, it is critical to develop improved diagnostic procedures to reduce these deaths. This object aims to develop an improved skin cancer diagnostic system that can have a positive impact on early detection of skin cancer. The key hypothesis is that single-scattered, polarized light spectroscopic methods combined with multiple-scattered, unpolarized light spectroscopy provide unprecedented tissue functional information and cellular structures for rapid noninvasive diagnosis of skin cancer. The hypothesis has been formulated on the basis of strong preliminary data produced with our combined Multiple Scattered Light Spectroscopy (MSLS)/Polarized Light Spectroscopy (PLS) prototype laboratory system. The rationale for the research is that a combination of MSLS/PLS technology can be used to accurately reflect morphologies in specific diseased layers of skin. The system achieved highly accurate results for skin cancer detection in a pilot clinical study, providing a specificity of 91%, relative to a specificity of 80% and 82% provided by using PLS and MSLS methods individually. Guided by strong preliminary data, this hypothesis is being tested from four perspectives. (1) An optical spectroscopic system combining single/multiple-scattered light measurements has been developed; (2) Reconstruction algorithms will be implemented to improve parameter extractions based on more accurate Hb/HbO2 calculation models, non-spherical particle scattering models and multi-modal particle size distribution models; (3) The system is being tested using simulation experiments, and human subjects; (4) Classification algorithms for skin cancer diagnosis will be developed by correlating optical signatures with the pathophysiologic parameters using histomorphometric techniques. The research is expected to significantly contribute to the early skin cancer screening and detection by maximizing cure rates and reducing and avoiding biopsies.

The research is supported by NIH Grant: 1 R15 CA131808-01

TTT-31

Biofunctionalized Nanoparticles and Graphene for Cell Imaging and Cancer Diagnostics – Yuehe Lin

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In this poster, we will describe the synthesis, biofunctionalization of nanoparticles and graphene. Nanoparticles and graphenes will be linked with DNA and antibodies for DNA assay, immunoassay for detection of cancer biomarkers and for in vivo cancer cell imaging.

TTT-32

A global endeavor towards primary prevention with the international breast cancer and nutrition (IBCN) project: Novel bioengineering-based detection and diagnostic initiatives – Sophie Lelievre

Sophie A Lelièvre[1,5], Ji-Xin Cheng[2,5], Joseph Irudayaraj[3,5], James F. Leary[1,5], Connie M. Weaver[4,5], and the IBCN core committee

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The alarming rise of breast cancer incidence in many low and middle income countries in the world and the lack of decrease of incidence in many high income countries, especially for younger women, have led the World Health Organization (WHO) to call for the development of primary prevention. During the first international breast cancer prevention symposium, in October 2010, Purdue University launched the International Breast Cancer & Nutrition (IBCN) initiative, the goals of which are to (i) foster the development of a global network on primary prevention research, (ii) promote collaboration with social science experts in order to provide avenues to propose and implement public health initiatives focused on primary prevention, and (iii) work on a specific common objective with partner countries from all regions of the world to understand the link between breast cancer types, epigenetic make-up and nutrition. This initiative requires the design of new methods to detect and precisely diagnose alterations that precede tumor development, measure breast cancer risk levels, and deliver and assess preventive therapies. Here we present bioengineering projects developed at Purdue University that will not only further the IBCN initiative but will also provide new techniques that can be applied for the detection and diagnosis of cancers in general. A first project is on nonlinear optical imaging detection of early alterations of the breast epithelium necessary for tumor development. Using chemical treatment as well as nutrients that can influence breast cancer development, we show that Raman spectroscopy can exquisitely measure changes in epithelial polarity by measuring lipid ordering, label-free, in live tissue structures. This technology opens the path to high-throughput screening of epithelial cancer risk and protective factors. A second project focuses on the delivery of paramagnetic submicrons particles via the breast ducts to detect and treat abnormal cells. We show the development of the first breast-on-chip system to test nanotechnology-based multiplex targeting approaches for improved early diagnosis of neoplasia. The third project aims at assessing epigenetic marks at specific gene loci using fluorescence lifetime microscopy-based single molecule analyses. We show that this technology can measure cellular heterogeneity in tissues, which brings new possibilities for better diagnostic procedures.

TTT-33

Efficient Circulating Tumor Cell Capturing in Microfluidic Devices – Yaling Liu

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This work aims to design and create a micro-patterned surface that will be integrated in microfluidic devices to enhance particle and CTC cell capture efficiency. Capture of ultralow concentration of circulating tumor cells in a blood sample is of vital importance for early diagnostics of cancer diseases. Despite the significant progress achieved in development of cell capture techniques, the enhancement in capture efficiency is still limited and often accompanied with drawbacks such as low throughput, low selectivity, pre-diluting requirement, and cell viability issues. The goal of this paper is to design a biomimetic surface that could significantly enhance particle/cell capture efficacy through novel multiscale computational model, 3D surface fabrication, and microfluidic testing.

TTT-34

Development of a compact, cost-effective spectroscopic imaging device for tissue absorption and scattering – Justin Lo

Justin Lo[1], Sulochana Dhar[1], Thomas Kuech[2], Nan Jokerst[1], Bing Yu[1], Nimmi Ramanujam[1]

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We present the development of a cost effective, compact optical spectroscopic imaging system for quantifying tissue absorption and scattering. The system operates under the principle of diffuse reflectance spectroscopy in the visible spectrum and aims to provide real-time visual maps of tissue composition using a fast, scalable inverse Monte Carlo model of reflectance. Diffuse reflectance spectroscopy (DRS) has been used as a tool to discern tissue types in many pre-clinical and clinical cancer studies of various organ sites. DRS is sensitive to the absorption properties of biological molecules, such as hemoglobin, ß-carotene, melanin, among others, as well as to tissue scattering, which can be attributed to cell density, morphology, collagen, etc. Much of the clinical validation in the DRS field have utilized systems consisting of broadband sources, fiber-optic probes, and expensive detection components, such as a CCD or PMT. While these systems have helped provide promising results in the research community for cancer diagnostics in clinical studies, they are not feasible for use in developing nations due to their cost and size. As an intermediate step to translating this technology for use in global health, we have developed a compact, low cost system, which consists of a broadband light source with an 8-slot filter wheel for illumination, and an array of silicon photodiodes for detection. Compared to the previous systems, it is smaller, less costly, and has comparable performance in extracting optical properties in tissue phantoms. The compact spectroscopic imaging system shows promise in providing real-time diagnostics for cancers of the head and neck, cervix, breast, and skin, which are all prevalent cancers in the developing world.

TTT-35

Statistically Significantly Improved Nodule Detection in Rib Suppressed Chest Radiography: – ShihChung Lo

Matthew Freedman[1], Shih-Chung B Lo[2], Scott Marshall[3], Christina M Bromley[3]

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Purpose: Through many technical endeavors, a computerized processing technique for chest X-rays (CXRs) has been developed to reduce bone opacity, while preserving original lung image textures and structures but equalizing the image contrast of the lungs. A software package (Soft Tissue Visualization or SoftView™) has recently been made and is commercially available. To determine the benefit of this computerized processing, we conducted a reader study where radiologists read standard chest X-rays (CXRs) alone (unaided) followed by bone suppressed images.

Material and Methods: Posterioranterior (PA) standard chest radiographs in 368 subjects (122 had confirmed lung cancer nodules) were used for this study. Fifteen Board Certified radiologists participated in this reader study. Each radiologist interpreted the standard image and then the bone suppressed image. Each reader recorded the location of the most suspicious nodule, if any, their level of suspicion and their recommendation for action (CT, Biopsy) if any. The read of the standard image alone was followed by a read of the bone suppressed image. Localized Receiver Operating Characteristic (LROC) curve analysis was used to evaluate the observers' performance by comparing the area under the curves. [Sample images revealing originally missed cancers will be presented on the poster.]

Results: The mean area under the LROC curves across all readers was 0.460 (95% CI: 0.435 to 0.486) for standard radiographs and 0.558 (95% CI: 0.539 to 0.578) after the reader viewed the bone suppressed images. The mean difference was -0.098 (95% CI: -0.116 to -0.080), a statistically significant improvement. Reader sensitivity increased from 49.5% on the standard chest radiograph to 66.3% with the aid of the soft tissue visualization processing. Specificity decreased from 96.1% to 91.8%.

Conclusion: The use of the soft tissue visualization processing was shown to statistically significantly improve radiologists' detection of lung nodules on chest radiographs.

Acknowledgements: Soft Tissue Visualization [SoftView™] was supplied by Riverain Medical, Miamisburg OH.

TTT-36

In silico Optical Physical Model (iPOM) of the cervical epithelium: a tool to facilitate the implementation of new optical technologies in low-resource countries – Calum MacAulay

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Successful implementation of new optical technologies for cervical cancer screening in low-resource countries depends on many factors. Developing a strong and shared scientific knowledgebase amongst researchers, scientists, engineers, and medical personnel that will work in concert to bring forward new devices in these settings is critical, as is having a means to hone work on new instruments. Herein, we present the in silico Physical Optical Model (iPOM), which is designed to simulate, analyze, and quantify the cell- and tissue-level biological changes that are associated with cervical preneoplastic growth. By reproducing these features, iPOM will also give insights into the ways in which dysplastic changes will be detected by different optical technologies being developed for cervical cancer screening. iPOM is derived from a database of quantitative histopathology images of the cervix. It depicts the 3D structure of the cervix at microscopic level, capturing spatial changes in cellular and nuclear morphology, tissue architecture, ploidy, inflammation, angiogenesis and biomarker expression in both the epithelium and stroma for each pathologically defined disease phase. HPV infection-associated changes are also evaluable. Based on electromagnetic light propagation models, iPOM can be used to predict how high resolution microscopy techniques will perform while analyzing clinical tissues. Ongoing analyses are using iPOM predicted results to guide acquisition of confocal images from clinical cervical tissues. Ultimately, this strategy will allow us to identify the most robust in vivo macroscopic imaging approaches for detection of cervical neoplasia and aid in determining which image features must be acquired to achieve accurate diagnoses (e.g. variations in excitation and emission wavelength, numerical aperture, polarization, etc.). In addition to honing instrumentation, iPOM can be used as a teaching tool for mapping out cell-level behaviors in cervical disease, offering a means for critical research personnel to learn about the biological mechanisms underpinning disease phenotypes.

This work was made possible through the support of NCI funding (P01-CA82710).

TTT-37

Density-Based Analysis with Magnetic Levitation – Katherine Mirica

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We developed a low-cost, rapid, and versatile method that uses magnetic levitation (MagLev) for analyzing relative differences in the chemical composition of a variety of substances based on density. We demonstrate the ability of this technique to compare the content of fat in food and milk, to determine salinity of water, and to monitor dynamic chemical processes (e.g., chemical reactions and binding interactions occurring on polymeric beads). The technique requires only a container filled with a paramagnetic solution (Mn(II) or Gd(III) in water), and two permanent NdFeB magnets oriented with like poles facing one another.

NIH, Bill and Melinda Gates Foundation

TTT-38

Capacitive Nanosensor for Multiplexed Molecular Detection of Biomarkers – Michael Naughton

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We report a novel nanoscale architecture for molecular detection based on arrays of coaxial capacitors that facilitate rapid and highly sensitive detection of target molecules. We demonstrate a detection limit for volatile organic compounds of ~150 parts per trillion in nitrogen at 20C, corresponding to ~ 30 molecules per sensor. The device exhibits wide dynamic range for such detection (> 5 decades in concentration). Fabricated from arrays of one million units per square millimeter, this sensor represents a unique route to all-electronic molecular-scale chemical detection, with potential utility in early-stage detection of cancer biomarkers.

This work is supported by NIH-NCI grant CA137681 and NSF grant PHY0804718.

TTT-39

High Definition Imaging of Circulating Tumor Cells and Associated Cellular Events in non-Small Cell Lung Cancer Patients; a longitudinal analysis – Jorge Nieva

Jorge Nieva[1], Marco Wendel[2], Madelyn Luttgen[2], Dena Marinucci[2], Lyudmila Bazhenova[4], Anand Kolatkar[2], Roger Santala[1], Brock Whittenberger[1], James Burke[1], Melissa Torrey[3], Kelly Bethel[2,3], Peter Kuhn[2]

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Sampling circulating tumor cells from peripheral blood is ideally accomplished using assays that detect high numbers of cells and preserve them for downstream characterization. We sought to evaluate a method using enrichment free fluorescent labeling of CTCs followed by automated digital microscopy in patients with non-small cell lung cancer. Twenty-eight patients with non-small cell lung cancer and hematogenously seeded metastasis were analyzed with multiple blood draws. We detected CTCs in 68% of analyzed samples and found a propensity for increased CTC detection as the disease progressed in individual patients. CTCs were present at a median concentration of 1.6 CTCs per milliliter of analyzed blood in the patient population. Higher numbers of detected CTCs were associated with an unfavorable prognosis.

This work was supported by the National Cancer Institute via research grants R01CA125653 and U54CA143906.

TTT-40

Low-cost microendoscopy for in situ identification of cervical neoplasia – Mark Pierce

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Cervical cancer is the second most common type of cancer in women worldwide, accounting for an estimated 493,000 incident cases and 273,000 deaths in the world in 2002. When detected early, cervical neoplasia is nearly 100% curable, but the resources required to implement widespread screening programs involving the Pap smear, colposcopy, biopsy, and treatment are often unavailable in developing countries. As a consequence, over 80% of deaths from cervical cancer occur in the developing world. Visual inspection of the cervix following application of acetic acid (VIA) is an effective screening method when colposcopy is not available, and can be incorporated with cryotherapy in single-visit "see-and-treat" protocols. However, in the absence of confirmatory biopsies, VIA is susceptible to poor specificity, leading to the unnecessary treatment of many benign lesions or conditions. We have developed a low-cost (<$1000) device which enables the healthcare provider to evaluate the cellular morphology of the cervical epithelium in situ and in real time. A 1mm diameter fiber-optic probe is placed in light contact with the cervix and transmits a high-resolution image of the underlying tissue to a laptop for display. The image resolves individual cells, enabling features such as nuclear crowding, enlargement, pleomorphism, and nuclear-to-cytoplasm ratio to be evaluated. We have carried out pilot in vivo studies with this device in the US, China, and Guatemala, totalling over 200 patients. By qualitatively and quantitatively comparing image features to the corresponding pathology diagnosis at each image site, we are evaluating the ability of the microendoscope to visualize the characteristic features of normal and neoplastic cervical epithelium and to rule-in or rule-out disease. This poster will present the latest findings from this ongoing study.

TTT-41

Low-cost microendoscopy for the diagnosis of esophageal squamous cell neoplasia in northern China: an evaluation of interobserver agreement and accuracy – Marion-Anna Protano

Marion-Anna Protano[1], Hong Xu[2], Fan Zhang[2], Steven Itzkowitz[1], Jonathan Potack[1], Mark Pierce[3], Peter Vila[1], Alexandros Polydorides[1], Michelle Kim[1], Jenny Sauk[1], Kalpesh Patel[1], Rebecca Richards-Kortum[3], Sharmila Anandasabapathy[1]

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Background: The incidence-to-mortality ratio for esophageal squamous cell cancer (ESCC) in high risk northern China remains a dismal 1:1 due to late diagnosis. Lugols chromoendoscopy is used for endoscopic screening in high-risk populations, but is limited by low specificity. Our group has created a low cost, battery-operated high-resolution microendoscope (HRME) that provides subcellular epithelial imaging after the application of topical proflavine to Lugols unstained areas. Methods: In this prospective clinical trial, 30 patients from the First University Hospital (Changchun, China) undergoing endoscopic screening for ESCC were enrolled. High-definition white light endoscopy and Lugols staining was performed, followed by topical proflavine 0.01% to Lugols-abnormal areas. After inserting the HRME through the accessory channel, optical and tissue biopsies were obtained. 163 optical sites were imaged; 45 images were used in a training set of 10 images, a test set of 39 images and 8 movies. Two experienced endoscopists with significant HRME experience (> 50 cases) and four novice endoscopists with no HRME experience completed the training and test set in a mixed, blinded fashion. Results: Among all endoscopists, the negative predictive value was 0.89 for still HRME images and 0.94 for movies. Sensitivity for cancer was 0.84 for images and 0.89 for movies and specificity was 0.77 and 0.87. The overall accuracy for images was 0.80 and for movies was 0.88. The accuracy for experienced endoscopists was 0.82 for images and 0.94 for movies; for novice it was 0.78 and 0.85. The kappa statistic for interobserver reliability for distinguishing dysplasia and ESCC from benign tissue in still images was kappa = 0.54 overall, and 0.69 in experts. Conclusion: HRME may be a cost-effective optical biopsy adjunct to Lugols screening for ESCC, potentially enhancing diagnostic accuracy, clinical yield, and real-time decision-making. Accuracy rates improved with experience and with the use of video images.

TTT-42

Integrated Microfluidic devices for Assays of Cancer Cell Migration, Invasion, and Protein Expression– Lidong Qin

Lidong Qin

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Integrated microfluidic devices, with ultra-miniaturized antibody arrays coated under micro-channels, are developed for the detection of cancer biomarkers from blood. Despite changes of plasma protein profiles reflect physiological or pathological conditions associated with many human diseases, only a few plasma proteins are routinely used in clinical tests. Reasons for this include the intrinsic complexity of the plasma proteome, the heterogeneity of human diseases and the rapid degradation of proteins in sampled blood. The integrated blood barcode chip can sensitively sample a large panel of protein biomarkers over broad concentration ranges and within 10 minutes of sample collection. Based on the same microfluidic technique, we also developed an approach that integrates on-chip cell handling and in situ protein secretion profiling. The platform enables us to assess the functional heterogeneity of single cells, with extensions to small cell colonies. We measured a dozen proteins secreted from human prostate cancer cell lines and correlation analysis showed the unusual protein regulation network for single cells, in comparison to traditional measurement on many cells system.

Dr. Lidong Qin is grateful for grant support from the Cancer Prevention and Research Institute of Texas.

TTT-43

Plasmon Coupling in Cancer Biomarker Detection and Quantification – Bjoern Reinhard

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The optical properties of noble metal nanoparticles are determined by the coherent collective electron oscillations of the conduction band electrons (the so called plasmons) in the particles. Noble metals nanoparticles are bright and since their signal is based on light scattering, instead of fluorescence, they do not blink or bleach. Through variation of the size and shape of the nanoparticles, their color can be modified in a rational fashion, which enables to label multiple features simultaneously. Noble metal nanoparticles are, however, not just very bright alternatives to organic labels. Noble metal nanoparticles have one additional interesting property that enables entirely new molecular imaging modalities: Plasmons in individual noble metal nanoparticles couple in a distance dependent fashion. Noble metal nanoparticles couple strongly on nanometer and tens of nanometer length scales; the spectrum of the coupled nanoparticles provides information about the local nanoparticle density. If the nanoparticles are selectively targeted at specific cell surface receptors, plasmon coupling can provide information about the local receptor density distribution in an optical microscope. In this poster we introduce to the fundamentals of plasmon coupling microscopy, discuss its experimental realization, and review the colloidal chemistry required for the synthesis of stable and selective noble metal nanoparticle immunolabels. We then apply this technology to quantify the EGFR density distribution on sub-cellular length scales.

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TTT-44

Microfluidic amperometric arrays for panels of cancer biomarkers – James Rusling

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A microfluidic electrochemical immunoassay system for multiplexed detection of protein cancer biomarkers was fabricated using a molded polydimethylsiloxane channel and routine machined parts interfaced with a pump and sample injector. Using off-line capture of analytes by heavily-enzyme-labeled 1 m superparamagnetic particle (MP)-antibody bioconjugates and capture antibodies attached to an 8-electrode measuring chip, simultaneous detection of cancer biomarker proteins prostate specific antigen (PSA) and interleukin-6 (IL-6) in serum was achieved at sub-pg mL-1 levels. MPs were conjugated with ~90,000 antibodies and ~200,000 horseradish peroxidase (HRP) labels to provide efficient off-line capture and high sensitivity. Measuring electrodes feature a layer of 5 nm glutathione-decorated gold nanoparticles to attach antibodies that capture MP-analyte bioconjugates. Detection limits of 0.23 pg mL-1 for PSA and 0.30 pg mL-1 for IL-6 were obtained in diluted serum mixtures. these system was also applied to the simultaneous measurement of 4 oral cancer biomarkers in patient serum. Protein biomarkers were measured in serum in total assay time 1.15 h and sensor array results gave excellent correlation with standard enzyme-linked immunosorbent assays (ELISA). These microfluidic immunosensors employing nanostructured surfaces and off-line analyte capture with heavily-labeled paramagnetic particles hold great promise for accurate, sensitive multiplexed detection of diagnostic cancer biomarkers.

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TTT-45

Development of the AV Avantage HPV E6 Test for Detection of Cervical Pre-Cancer and Cancer in Low-Resource Settings – Johannes Schweizer

Berard-Bergery, M[1], Mahoney, CW[1], Silver, JE[1], Henry, P[1], Ho, M[1], Ramasamy, V[1], Tajan, E[1], Bisht, A[1], Jeronimo, J[2], Peck, RB[2], Weigl, BH[2], Gravitt, P[3], Howard, R[3], Castle, P[4], Lu, PS[1], and Schweizer, J[1]

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Cervical cancer is one of the leading causes of cancer-related morbidity and mortality of women worldwide, with ~ 80% of the ~250,000 yearly worldwide deaths occurring in low-resource settings. If detected at the pre-cancer stage, clinical intervention is effective in preventing invasive cancer to develop. Implementation of broad screening programs for cervical neoplasia resulted in a striking decrease in cervical cancer mortality in many developed countries, underlining the impact of appropriate cervical cancer screening. The screening strategies used (Pap Test followed by colposcopy and biopsy of positives), however, are not appropriate for broad and effective use in limited resource settings, due to the overall low clinical sensitivity and specificity, and the need for complex infrastructure.

Arbor Vita Corporation, in collaboration with PATH, has developed the AV Avantage HPV-E6 Test (HPV E6 test) for detection of cervical pre-cancer and cancer in low-resource settings. The test detects elevated levels of the HPV-E6 oncoprotein. HPV-E6, in concert with HPV-E7, is a necessary causing agent for cervical high-grade pre-cancer and cancer to develop, and therefore the use of E6 as a marker would achieve high clinical sensitivity and specificity. The HPV E6 test promises therefore to identify those women who are in need of clinical follow-up among the many more women who have HPV infections without clinical consequences. The HPV E6 test uses the lateral-flow (strip-test) format, allowing for a simple and robust workflow (no complex equipment needed) and for stability of test storage (no cold chain required). The HPV E6 test's potential for high clinical specificity has been demonstrated in clinical pilot studies, and the test is currently taking part in a large clinical validation study in China (START-UP), developed by PATH and the Chinese Academy of Medical Sciences.

An overview presentation on principle and workflow of the HPV E6 test, and on data from the clinical pilot studies will be given.

TTT-46

Multiplexed reconfigurable biomarker detection using solid-liquid phase change nanoparticles – Ming Su

Chaoming Wang, Liyuan Ma, Ming Su

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We have developed a multiplexed reconfigurable method to detect biomarkers using solid-liquid phase change nanoparticles.1-4 This new signal transduction method uses a previously-unexplored thermal property of solid materials to readout binding events of biomarkers: the temperature of a solid does not rise above its melting point until the entire solid is molten, and the solid will have sharp melting peak in thermal analysis using differential scanning calorimetry. The solid materials are pure metals or eutectic alloys of selected metals, and will be made into nanoparticles using colloidal method. A one-to-one correspondence can be created between one type of biomarker and one type of nanoparticle (Figure 1). The biomarker identification is converted to detection of solid to liquid phase transitions of according nanoparticles, where the sharp melting peaks, large thermal scan range, and wide choice of nanoparticles enable high multiplicity and sensitivity.

By combining plentiful phase diagram knowledge gained in the past hundreds years with size advantage of nanoparticles, thermal biosensing has shown several distinct features for biomarker detection: (1) high multiplicity owing to sharp melting peaks, large thermal scan range, and rich materials choice; (2) high sensitivity due to large latent heats of fusion of selected materials, and controlled grafting density of ligand at nanoparticles; (3) wide detection range for multiple biomarkers whose concentrations differ few orders of magnitude; (4) simultaneous detections of multiple DNA and protein biomarkers contained in complex fluids with minimal sample preparation; (5) thermal barcodes with ultrahigh labeling capacity can also be generated; and (6) statistically-significant number of detection results for multi-parameter based discrimination. By filling knowledge gap among biosensing, metallurgy and nanotechnology, the thermal biosensing using solid-liquid phase transitions of nanoparticles represents a paradigm shift from existing electric, electronic, magnetic, or photonic systems, and will bring new capabilities for biomarker based disease detection.

TTT-47

Detecting Cervical Dysplasia in Minority Populations using Raman Spectroscopy – Elizabeth Vargis

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Over the past few years, we have developed a probe-based instrument to acquire Raman spectra from the cervix in vivo. Raman spectroscopy is an optical technique that measures the vibrational and rotational properties of bonds, many of which are found in biological samples. As a molecular specific technique, Raman spectroscopy can provide detailed information about the biochemical composition of a tissue sample. In this study, we acquired Raman spectra from the cervix of a diverse group of patients undergoing a Pap smear or colposcopy-guided biopsy. For the Pap smear patients, the sterilized probe was placed directly onto the cervix in various locations for 2-3 seconds. For the colposcopy-guided biopsy patients, the probe was placed on one normal area and any area(s) the doctor decided to biopsy. Next, a sophisticated algorithm was used to classify tissue spectra as normal or negative for disease, metaplasia, low-grade, or high-grade dysplasia. This classification was then compared to the report from pathology. Previous results show that our tool works with a sensitivity of 98% and a specificity of 96%, with high-grade spectra classifying correctly 95% of the time and low-grade data classifying correctly 74% of the time. Analysis of this more diverse patient population shows more varied results, due to race/ethnicity, BMI, parity and insurance. Parsing the data based on these normal patient variables leads to sensitivity, specificity, and classification rates between 95% and 100% for all categories. The results of using this non-invasive tool directly on patients from varying socioeconomic and ethnic/racial backgrounds show its benefit in any setting where professional medical care is difficult to achieve.

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TTT-48

Optical property measurement in layered tissues: Discrimination between normal and dysplastic mucosa phantoms – Quanzeng Wang

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Approximately 50% of cancers diagnosed worldwide originate in mucosal tissues such as those lining the lungs, colon, esophagus, cervix, oral cavity and bladder. Ultraviolet-visible (UV-Vis) spectroscopy and spectral imaging have demonstrated great potential for providing minimally invasive detection of mucosal neoplasia, however, consistently high accuracy levels remain elusive and devices often rely on parameters or signals that are not well understood. *In vitro* studies have indicated that layer-specific changes in the fundamental optical properties (OPs) of mucosal tissues – absorption and scattering coefficients – occur during carcinogenesis. Therefore, the intent of this study was to develop a simple fiberoptic approach for rapid, *in situ* determination of UV-Vis OPs of individual mucosal tissue layers with dual-use potential: elucidation of light-tissue interactions and discrimination of normal and dysplastic mucosa. Specifically, we have assessed an approach involving multi-fiber diffuse reflectance spectroscopy coupled with neural network (NN) inverse models for estimating OPs in layered turbid media. The NN models were trained on data generated from over 20,000 Monte Carlo simulations. Nonlinear fitting based on known tissue absorption and scattering signatures was performed to reduce variability and optimize predicted OP values. Experimental measurement of two-layer phantoms was performed at 350-600 nm. To simulate normal and neoplasia mucosal tissues, agarose-based solid phantoms with 0.22 and 0.44 mm thick superficial layers were constructed with India ink, hemoglobin and polystyrene microspheres. Experimental results indicated that OPs could be estimated with mean errors of 21-38% and that discrimination between normal and neoplastic phantoms was easier to achieve when the superficial layer was 0.44 mm thick. These results provide strong evidence that our approach to measurement of layered tissue optical properties using relatively basic instrumentation may also enable detection of mucosal neoplasia.

Key words: Optical property, broadband light source, neural network, Monte Carlo, numerical modeling, two-layer tissue, mucosal tissue, reflectance, light-tissue interaction

TTT-49

Malignant Tumor Detecting System using Tactile Images – Chang Won

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Characterizing and locating sub-surface inclusions will greatly enhance the detection and treatment of breast cancer. A novel tactile imaging system that is capable of detecting and characterizing the sub-surface object, was designed, implemented, and tested. This system estimates the size, depth, and Youngs modulus (elasticity) of the tumors. The developed system is simple, relatively low-cost, portable, and effective. A Polydimethylsiloxane (PDMS) optical waveguide has been fabricated as the sensing probe. The light was illuminated below the acceptance angle to totally reflect within the flexible and transparent waveguide. When the sensing probe is compressed by an external force, the contact area of the probe deforms and causes the light to scatter. The scattered light is captured by a high resolution camera and saved as an image. Using the salient features of the captured image, we estimated inclusion characteristics such as size, depth, and Young's modulus. Larger and stiffer tumors are more likely to be malignant. Thus, we utilize the mechanical properties of the tumors to warn against malignant tumors. To test the performance of the proposed system, we utilize realistic tissue phantoms with embedded stiff inclusions. The experimental results showed that the proposed system can detect inclusions and provide the relative values of inclusion's mechanical properties. Using these relative values, we distinguish between malignant and benign tumors. Finally, we present pilot human tumor study results.

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TTT-50

Accuracy of optical spectroscopy for the detection of cervical intraepithelial neoplasia and the role of probe placement – Jose-Miguel Yamal

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Optical spectroscopy has been proposed as an accurate and low-cost alternative for detection of cervical intraepithelial neoplasia. We previously published an algorithm using optical spectroscopy as an adjunct to colposcopy and found good accuracy (100% sensitivity, 71% specificity). Those results depended on measurements taken by an expert colposcopists as well as the colposcopy diagnosis. In this study, we trained and tested an algorithm for the detection of cervical intraepithelial neoplasia that did not include the colposcopic diagnosis. Furthermore, we explored the interaction between spectroscopy and colposcopy, examining the importance of probe placement expertise. The colposcopic diagnosis-independent spectroscopy algorithm had a sensitivity of 0.98 [95% confidence interval (CI) = 0.89 1.00] and a specificity (correctly identifying those patients who had histology reading CIN 1 or better) of 0.62 [95% CI = 0.52 - 0.71]. The difference in the partial area under the ROC curves between spectroscopy with and without the colposcopic diagnosis was not statistically significant (p=0.43). Additionally, spectroscopy accuracy was independent of the placement expertise of colposcopists.

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TTT-51

Eddy Current Measurement: A Novel Tool for Detecting Cancer – Emily Sequin

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A majority of solid malignancies are treated by surgical resection. Determination of surgical margins is important in minimizing recurrence of the disease. In current clinical practice, less than 1% of the resected specimen undergoes microscopic examination, making the quantitative determination of surgical resection margins imprecise. We present a method that exhibits potential for distinguishing cancer from normal tissue by interrogating the characteristics of eddy currents induced in the tissue. Eddy current detection is well known in the materials science community for detecting the presence of flaws in materials, but this technique has not been used in the analysis of biological tissue. Using a device (referred to here as an electromagnetic or EM probe) comprising coils resembling the primary (driver) and secondary (detector) sides of a transformer, the voltage on the detector is measured using phase-lock detection when the probe is placed on the surface of tissue. The driver coil induces eddy currents in the tissue whose magnetic fields then interact with the EM probe. Measurements on closed conducting metal wire loops reveal that the phase of the voltage induced in the detector coil is dependent both on the conductivity of the tissue as well as its morphological structure manifested as eddy current domains. Proof-of-principle ex-vivo measurements on animal tissue and surgically excised human tissue specimens show that cancer can be clearly distinguished from surrounding normal tissue. The measurements described here may be useful in verifying the adequacy of surgical margins and in imaging the resected specimen in real-time in the operating room as a complement to histopathological analysis.

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TTT-52

Aptamer Functionalized Microcantilever Based Sensing Approach for Small Molecules – Pranav Shrotriya

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We report a microcantilever based novel sensing mode for detection of small molecules such as cocaine that achieves same detection threshold as immunoassays but in much shorter time. The novel sensing mode relies on resolving the rate of dissociation of aptamer/ligand complexes on the sensing surface. In the absence of ligand, the dissociation of the ligand /aptamer complexes is limited by the diffusion of aptamers away from the cantilever surface however in presence of ligand the aptamers are consumed by both diffusion and reaction leading to accelerated dissociation rates. Hence resolving the rate of ligand/aptamer complex dissociation may be used to detect the presence of ligand molecules. In order to implement the sensing strategy, cocaine and its known aptamer are chosen as a model system. The cocaine/aptamer complexes are immobilized on only one side of a microcantilever. Surface stress change associated with the formation of cocaine/aptamer complex induces a large bending of the microcantilever. Dissociation of the complexes results in relaxation of the surface stress and thus reduction in cantilever bending. During the sensing experiments, the cocaine/aptamer complex coated cantilever is introduced into solutions of different cocaine concentrations and the cantilever bending is monitored to determine the rate of complex dissociation on the cantilever surface. Experimental results indicate that the rate of cantilever bending demonstrates an excellent correlation with the cocaine concentration and demonstrate a sensing threshold of 100 ng/ml of cocaine concentration in phosphate buffered saline solution. These results demonstrate that the novel sensing mode for aptamer functionalized microcantilevers can provide an invaluable tool for detection because of its portability, capability for detection and identification with high sensitivity and specificity.

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TTT-53

Atomic force microscopy as a prospective tool in the detection of cancer cells – Igor Sokolov

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Humans are still far from conquering cancer with traditional biochemical methods. There is a hope that physical sciences could bring new insights and provide new ways to attack on cancer. With the development of nanoscience and nanotechnology, scientists have obtained a new set of instruments to study physics of cancer at the nanoscale. Here we will describe the study of various physical properties of human cervical epithelial cells, and their transformation during progression to cancer. Using physical (non-specific) labeling with fluorescent silica particles and atomic force microscopy (AFM), we found interesting physical differences between the surface of normal and cancerous cervical cells. To characterize the cell surface layer quantitatively, we used AFM, a technique that allows studying mechanics of biological cells in their native environment. We found that the brush layer (microvilli, microridges, glycocalyx) on the surface of cancer cells was more heterogeneous and substantially less dense than in the case of normal cells. Furthermore, using the AFM imaging of the surface of fixed cells, we observed an intriguing emergence of fractal behavior on the surface of cancerous cells. This leads to an unusually high accuracy in identification of cancer at the single cell level, which is virtually 100% as tested in vitro on ~300 cells collected from 12 humans. Our results suggest that the fractal dimensionality could be used a fundamentally new potential biomarker for early detection of cervical cancer cells with accuracy and specificity surpassing existing methods. References 1. Iyer, S., C.D. Woodworth, R.M. Gaikwad, Y.Y. Kievsky, and I. Sokolov. Small, 2009. 5: p. 2277 - 2284. 2. Iyer, S., R.M. Gaikwad, V. Subba-Rao, C.D. Woodworth, and I. Sokolov. Nature Nanotechnology, 2009. 4: p. 389-393. 3. M. E. Dokukin, N. V. Guz, R. M. Gaikwad, C.D. Woodworth, I. Sokolov. Phys. Rev. Lett. in press

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TTT-54

Toward Fluorescence Imaging of Breast Cancers with Newly Developed Carbon Dots – Ya-Ping Sun

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Fluorescence-based optical imaging has emerged as a highly promising technique for potentially the early detection and diagnostics of breast cancers (more so than those associated with internal organs or requiring much deeper tissue penetration), and also in the cancer treatments (such as tumor profiling in surgery and imaging-guided drug delivery, among others). Critical to the technique is the development of highly sensitive and specific imaging agents. For potent imaging agents, the rationale for the use of semiconductor quantum dots (QDs) over organic dyes is now generally accepted in the community. However, the potentially prohibitive limitation for the semiconductor QDs is the necessary use of heavy metals such as the highly toxic cadmium. We found that small carbon nanoparticles could be surface-passivated with organic or bio-molecules to exhibit similar optical properties to those found in semiconductor QDs. Our study has produced significant evidence suggesting that these carbon-based quantum dots or carbon dots are not only non-toxic in vitro and in vivo, but also performance-wise competitive to the commercially supplied CdSe/ZnS QDs. In fact, ever since our first report on carbon dots, a sizeable community including many research groups worldwide has emerged, with studies looking into all aspects of these new fluorescent nanomaterials. Collectively the results have consistently confirmed our original finding that carbon at the nanoscale can be made brightly fluorescent in multiple colors. In this talk, some representative experimental results obtained in our laboratory on carbon dots as optical imaging agents and their uses in fluorescence imaging in vitro and in vivo will be presented, along with discussion on applications of the technology to breast cancer research and therapy.

NIH, Susan G. Komen for the Cure, and DoD/BCRP.

TTT-55

The Terahertz Magnon Photon Laser Imaging System (TERMAPLIS) – Boris Tankhilevich

Boris Tankhilevich[1] and Yehiel Korenblit[1]

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The new Terahertz Magnon Photon Laser Imaging System (TERMAPLIS). is expected to output THz power up to 10 mW for a one stage device (and up to 1 watt for a fully developed system having up to 100 stages) (that is 106 times more than 1 nanowatt power output from contemporary THz generators) and is expected to be fully tunable within the 10% window around the main frequency by changing the amplitude of the applied longitudinal magnetic field (up to 2 Tesla), or a biased electric field (having the same order of magnitude as a regular PNP transistor). (1-2) Thus, the new TERMAPLIS will be able to support THz imaging of the boundaries between the cancerous and healthy tissues with a much higher spatial resolution (supported by tunability) and would also improve SNR ratio available in other devices due to high power output that is unique to this invention. Therefore, the proposed TERMAPLIS would provide an enabling tool capable of aiding a surgeon in immediately identifying residual cancer after the main tumor has been removed, thus guiding further surgery particularly in the marginal zone of breast and other tumors. [1] B G Tankhilevich and Y Korenblit 2011 J. Phys.: Conf. Ser. 263 012004 [2] Korenblit Y and Tankhilevich B ; 2008 Generation of terahertz waves US Patent 7,430,074; 2008 Tunable generation of terahertz radiation US Patent 7,440,178; 2008 Method and apparatus for generating terahertz radiation with magnon gain medium and magnon mirror US Patent 7,471,449; 2009 Magnon laser US Patent 7,508,578; 2010 Modulation of Terahertz radiation US Patent 7,706,056

Professor Thomas F. Budinger is acknowledged for his role in understanding of benefits provided by Terahertz Magnon Photon Laser Imaging System (TERMAPLIS)

TTT-56

Label-free Biomarker Detection with Quartz Nanopipettes – Boaz Vilozny

Boaz Vilozny, Paolo Actis, R. Adam Seger, Nader Pourmand

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Artificial nanopores are an emerging technology for label-free detection of cancer biomarkers. Our group has developed electrical sensors based on a quartz nanopipette capable of detecting biomolecules in ultra-low volumes of liquid. The nanopipette is a quartz needle with a nanoscale pore at the tip. An electrical signal is generated as electrolyte fluids pass through the pore, which can also accommodate proteins and small molecules. By immobilizing receptors such as antibodies, aptamers, and ligands to the surface of the nanopore, proteins and other biomarkers can be selectively targeted. We are currently working to improve the surface chemistry for rapid and robust conjugation of receptors to target cancer biomarkers with enhanced sensitivity and dynamic range. In addition to these single-pore sensors, we are developing arrays of nanopores for multiplexed detection in complex fluids. We will present our recent results as well as ongoing research in the field of cancer diagnostics with nanopore sensors.

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TTT-57

Isolation and enrichment of cancer cells – Guiren Wang

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Isolation and enrichment of cancer cells from other cells could significantly enhance sensitivity and specificity of cancer detection, since the cancer cell number is limited for early cancer diagnosis. Although there have been many publications on the cancer cell separation from other cells, one type cancer cell separation and isolation from other type cancer cells is yet to be investigated. Separation of different cancer cells is important in detecting circulating tumor cells. However, separation of different cancer cells is difficult, since they have similar size and are mostly epithelial cells. We use dielectrophoresis (DEP) in a microfluidics platform to study isolation and enrichment of cancer cell lines, such as colorectal cancer cell HCT-116, prostate cancer cell LNCap and breast cancer cell MCF-7 respectively. It is found that HCT-116 can be separated from normal Human Embryonic Kidney 293 cells (HEK-293). It is also found that LNCap and MCF-7 can be separated from HCT-116 respectively under different conditions, i.e. AC frequencies. Such a capability demonstrates the high specificity of DEP for cell isolation and separation, and could provide new biomarkers. Furthermore, to increase purity and throughput of the DEP separation, cascade and staggered DEP sorters are developed respectively. Particle and cell separation indicates that the cascade DEP cell sorter can significantly enhance the purity of the targeted cells for diagnostics; The staggered DEP sorter can largely increase sample throughput without compromising the purity to overcome the common issue related to microfluidic device. The results could provide a new opportunity for sample preparation in early cancer diagnosis.

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TTT-58

Quantum Dots and Single Molecule Detection Technologies for Highly Sensitive Detection of Circulating DNA Cancer Markers in Clinical Samples – Jeff TH Wang

Tza-Huei Jeff Wang

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Genomic analysis of biomarkers, including genetic markers such as point mutations and epigenetic markers such as DNA methylation, has become a central theme in modern disease diagnosis and prognosis. Recently there is an increasing interest in using single-molecule detection (SMD) for genomic detection. The driving force not only comes from its ultrahigh sensitivity that can allow the detection of low-abundance nucleic acids with reduced or without the need of amplification but also from its potential in achieving high-accuracy quantification of rare targets via single-molecule sorting. The unique photophysical properties of semiconductor quantum dots (QDs) have made them ideal for use as spectral labels and luminescent probes. QDs also make excellent donors to pair with organic dyes in the fluorescence resonance energy transfer (FRET) process due to the features of narrow emission spectra and small Stokes shift. This enables FRET with minimal direct acceptor excitation and donor-acceptor crosstalk, thereby permitting the design of FRET molecular sensors with extremely low intrinsic fluorescence backgrounds necessary for detecting biomolecular targets at low abundance. We have developed highly sensitive, quantitative and clinically relevant technologies for analysis of genomic markers based on the convergence of SMD, microfluidic manipulations, and quantum dot fluorescence resonance energy transfer technology (QD-FRET). Extraordinary performances of these new technologies have been exemplified by analysis of a variety of biomarkers including point mutations, DNA integrity and DNA methylation in clinical samples.

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TTT-59

Microwave Induced Thermal Acoustic Imaging and Spectroscopy for Potential Breast Cancer Detection – Hao Xin

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Microwave-induced thermal acoustic imaging (TAI) is an emerging technique that may have great potential in many biomedical applications. It has the advantages of being simpler and having much higher resolution than traditional microwave imaging as well as having much better contrast than traditional microwave imaging as well as having much better contrast than traditional ultrasound imaging. we evaluate the feasibility of a novel microwave induced thermaoacoustic imaging and spectroscopy (TAIS) instrument incorporating a one-of-kind microwave source with flexible pulse width that can generate a very short pulse (from $\leq$ 50 ns to 1 s, versus 0.5 s in reported studies) to achieve 5 to 10 times higher imaging resolution than the current state-of-the-art. Most important, instead of operating at a single microwave frequency, this instrument will operate from 2.7 to 3.1 GHz and 5 to 9 GHz (potentially as low as 2 GHz to as high as 15 GHz) with continuous tunability in order to maximize detection specificity and enable spectroscopy capabilities. Accurate electromagnetic model utilizing existing computer aided design (CAD) tools will be utilized and combined with rigorous acoustic simulation to design and optimize the interaction of microwave pulse and biological sample to achieve best diagnosis performance. Our initial simulation results based on measured microwave properties of different breast tissues have demonstrated that much higher specificity and SNR can be potentially obtained with TAIS compared to traditional TAI at just one frequency.

TTT-60

A New FIRMS Technique for Molecule-Specific Magnetic Imaging of Cells – Shoujun Xu

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Magnetic particles are widely used in molecular and cellular imaging. Compared to optical imaging that can use wavelength to achieve molecular specificity, magnetic-field signal cannot be resolved into a group of individual signals based on molecular specificity. To solve this problem, we develop a technique based on the binding force between the ligand-conjugated magnetic particles and the receptor molecules on cells. This force-induced remnant magnetization spectroscopy (FIRMS) measures the magnetization of the magnetic nanoparticles as a function of the binding force between the magnetically-labeled probe molecules and the target molecules. Molecular specificity is achieved from the spectrum of magnetization vs. binding force. To provide spatial information of magnetically labeled molecules and cells, the classic inverse problem is encountered, i. e., the spatial information is not a unique solution to the measured magnetic signal. To solve this problem, we recently developed a scanning magnetic imaging (SMI) technique, which scans the sample across a magnetic sensor. From the magnetic field profile, the spatial information and the magnetization of the magnetically-labeled molecules can be obtained simultaneously. Currently we have achieved spatial resolution of 20 micrometers at a detection distance of nearly 1 cm. We have investigated specific cellular uptake of ligand-conjugated magnetic particles, in which the physisorbed particles and cell-bound particles are resolved without sample separation. We have also studied force-induced -mouse IgG bond andαrupture of two different noncovalent bonds: mouse IgG biotinstreptavidin bond. Rebinding experiments were performed to confirm the specific dissociated bonds, a unique advantage over single-molecule techniques such as optical tweezers and atomic force microscopy. A new theoretical model is proposed to interpret experimental findings. Further development of the techniques and future applications will be presented.

TTT-61

Single Cell Assay Chips for Cancer Drug Screening and Pairwise Cell-to-Cell Interactions – Euisik Yoon

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The heterogeneity of cancer cells has been given attention because malignant sub-phenotypes such as cancer stem cells could be identified for effective treatment. To facilitate the heterogeneity study in a low cost and highly efficient manner, we developed a microwell array chip capable of culturing single cells into their colonies for recognizing different sub-phenotypes and introducing test-reagents to the clones for characterization. Our prototype allowed us to track each single-cell progeny for differences in proliferation and morphology, and was able to successfully identify three different sub-phenotypes in PC3. It also successfully measured differences in drug responsiveness and correlate them to cell phenotypes, showing clear and repeatable differences in drug response between them. Understanding cell to cell interactions is critical for applications in tissue engineering, and stem cell and cancer therapy. While this is an area of prolific research, little has been done to integrate multiple separate aspects of cell interaction, focusing solely on co-localization of single cells or accumulation of secreted factors. We present a microfluidic platform capable of arranging cell pairs, controlling arraignment proximity, and dynamically altering isolation states to cause the buildup or washing-away of secreted factors. This device allows for the comprehensive and high-throughput analysis of contact and secretion based interactions occurring between cell pairs. Two cell lines, C2C12 (a myoblast cell line) and PC3 (a prostate cancer cell line that secretes VEGF and bFGF) were co-cultured in the dynamic isolation microfluidic platform. The proliferation rates of C2C12 cells are significantly increased (approximately double) when cells are paired with a PC3 cell, as compared to the negative control, when paired with another C2C12 cell.

NIH NCI SPORE, KAUST, NSF, Thermo Fisher Scientific

TTT-62

Chemometrics based image processing and delineation for the intraoperative mapping of nonmelanoma skin cancer – Seongkyu Yoon

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Nonmelanoma skin cancers are one of the most common human cancers and their occurrence has been increasing at a remarkable rate. Most nonmelanoma skin cancers are curable by surgery. However, delineation of tumor margins during surgery is challenging due to the poor visual contrast. Over the last decades, various optical imaging techniques have been developed to aid intraoperative inspection of skin cancers. For example, reflectance and fluorescence polarization imaging has been demonstrated to provide accurate real-time and cost-effective method for skin cancer demarcation. This study will investigate the feasibility of further improving the efficiency of the reflectance polarization imaging by application of the chemometric analysis. The spectral pattern of optical images obtained from tumors can be used to discriminate them from healthy tissues or assist in localization of cancer margins. Typically, spectra from optical imaging measurements have tremendous information about the biological state of samples and the availability of this information is highly suited for a multivariate approach of chemometrics. The main challenge in biomedical application of chemometrics is a construction of simple, robust and accurate classification models including the tasks of raw spectra preprocessing, feature selection, model validation, etc. In this study, delineation performance of nonmelanoma skin cancers as an intra-operative tool will be addressed by using the proposed chemometrics-based image processing approach. In the previous research, feasibility of combination of multimodal reflectance and fluorescence polarization imaging (RFPI) with spectroscopic analysis of the reflectance images was investigated for intraoperative delineation of basal cell and squamous cell carcinomas and the spectral responses including the optical densities as well as their wavelength derivatives were calculated for assessment of benign and malignant stained skin structures. This study will investigate if delineation performance can be improved by using chemometrics based image processing methods. In order to increase the accuracy of classifying tumors and other healthy structures, several chemometrics techniques will be tested, including orthogonal partial least squares-discriminant analysis (OPLS-DA), support vector machine (SVM), etc. with combination of novel feature selection methods

TTT-63

A smart fiber optic sensor for detection of oral and cervical cancer in developing world – Bing Yu

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Each year, over 481,000 new cases of oral cancer are diagnosed worldwide, with a 5-year mortality of ~50% and nearly two-thirds of which occurs in developing world. Cervical cancer is the second most common cancer in women with an incidence and death rate of 16 and 9 per 100,000 women, respectively, and 80% of cases occur in the developing world. The high death rate in developing countries is largely due to the fact that these countries do not have the appropriate infrastructure and resources to support the organized screening and diagnostic programs that are available in the U.S. The optical absorption and scattering properties of epithelial tissues reflect their underlying physiological and morphological properties. Diffuse reflectance spectroscopy (DRS) with a fiber optic probe can be used to noninvasively quantify these tissue properties and has shown promise for diagnosis of early precancerous changes in the cervix and oral cavity by our group as well as others. However, current DRS techniques are susceptible to several sources of systematic and random errors, such as uncontrolled probe-to-tissue interface and lack of a real-time calibration that can influence the robustness of this technology in resource-poor settings. These systems also use bulky, high power and expensive optical components, such as thermal light sources, spectrographs, and cooled CCD cameras, which need a stable power supply. In this poster we report the development of a portable, easy-to-use and low cost, yet accurate and reliable DRS device that can aid in the screening and diagnosis of oral and cervical cancer at an early stage and that is well suited for use in a low-resource setting. The device uses an innovative smart fiber-optic probe to eliminate operator bias, state-of-the-art photonics components to reduce power consumption, and automated software to reduce the need of operator training.

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TTT-64

Development of an ultrasound-mediated fluorescence imaging technique for cancer detection – Baohong Yuan

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Ultrasound and fluorescence optical imaging techniques are two commonly used and cost efficient biomedical imaging techniques. However, each of them suffers from their disadvantages. For examples, fluorescence techniques have high molecular sensitivity and specificity but poor spatial resolution in deep biological tissues. Ultrasound techniques can provide much higher spatial resolution than fluorescence optical techniques but suffer from low molecular sensitivity and specificity. To overcome these limits, we are developing a new hybrid imaging technique that is based on physical interaction between ultrasound wave and fluorescent molecules: ultrasound-mediated fluorescence imaging technique. This hybrid technique can provide optical contrast images with ultrasonic spatial resolution. The potential applications of this technique include high resolution imaging of cancer in breast, prostate, thyroid, skin, head and neck. Because both ultrasonic and optical imaging techniques are relatively cost efficient, this new imaging technique are affordable and can be potentially used in low-income and middle-income countries.

We acknowledge the funding support of National Institute of Health (Contract number 7R15EB012312-02).

TTT-65

Immunomagnetic Nano-Screening Chip for Circulating Tumor Cells Detection in Blood – John X.J. Zhang

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We present a novel method towards diagnose cancer at an early stage via a blood test. Early diagnosis is high on the future agenda of oncologists because of significant evidence that it will result in a higher cure rate. Capture of circulating tumor cells (CTCs) which are known to escape from carcinomas at an early stage offers such an opportunity. We design, fabricate and optimize the nanomagnetic-screening chip that captures the CTCs in microfluid, and further integrate the nano-chip with the new multispectral imaging system so that it can quantify different tumor markers and automate the entire instrument. Specifically, hybrid plasmonic (Fe2O3-core Au shell) nanoparticles, conjugated a collection of antibodies especially chosen to target breast cancer CTCs, with high magnetic susceptibility will be used for effective immunomagnetic CTC isolation. Greatly increased sensitivity over previous attempts is demonstrated by decreasing the length scale for interactions between the magnetic-nanoparticle-tagged CTCs and the isolative magnetic field, while increasing the effective cross-sectional area over which this interaction takes place. The screening chip is integrated with a novel hyperspectral microscopic imaging (HMI) platform capable of recording the entire emission spectra in a single pass evaluation. The combined system will precisely quantify up to 10 tumor markers on CTCs.

NATIONAL CANCER INSTITUTE (1R01CA139070)

TTT-66

Magnetic nanoparticle hyperthermia: In vivo heating experiments using implanted prostatic tumors and microCT imagings of nanoparticle distribution – Liang Zhu

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Among a variety of hyperthermia methods, magnetic nanoparticle hyperthermia is a highly promising approach for its confined heating within the tumor. In this study, we perform in vivo animal experiments on implanted prostatic tumors in mice to measure temperature distribution in the tumor during magnetic nanoparticle hyperthermia. Temperature elevations are induced by a commercially available ferrofluid injected via a single injection to the center of the tumor, when the tumor is subject to an alternating magnetic field. Temperature mapping in the tumors during magnetic nanoparticle hyperthermia has demonstrated the feasibility of elevating tumor temperatures higher than 50C using only 0.1 cc ferrofluid injected in the tumor under a relatively low magnetic field (3 kA/m). Detailed 3-D nanoparticle concentration distribution is quantified using a high-resolution microCT imaging system. The calculated nanoparticle distribution volume based on the microCT scans is useful to analyze nanoparticle deposition in the tumors. Slower ferrofluid infusion rates result in smaller nanoparticle distribution volumes in the tumors. Therefore, nanoparticles are more confined in the vicinity of the injection site with slower infusion rates, causing higher temperature elevations in the tumors. The increase in the nanoparticle distribution volume in the tumor group after the heating from that in the tumor group without heating suggests possible nanoparticle re-distribution in the tumors during the heating.

This research is supported in part by an NSF research grant CBET-0828728, an NSF MRI grant CBET-0821236, and an research grant from the University of Maryland Baltimore County (UMBC) Research Seed Funding Initiative. The research is performed in partial fulfillment of the requirements for the Ph.D. Degree from UMBC by Anilchandra Attaluri.

Poster Abstracts:

Global Health and Epidemiology of Cancer

GGG-67

Focus Group Findings in the Use of Technology in Reaching African American Women with Breast Cancer Messages – Dee Baldwin

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As more and more individuals and organizations use the Internet and websites for communicating information about medical conditions, more studies are needed to examine the effects of different technological techniques (Internet, websites, touch screens, music-CDs, and interactive CD-ROMs) to determine their usefulness with clients of diverse backgrounds. While many patients from diverse culture groups can access different breast cancer educational sources, they still experience barriers in their attempt to access health care. The purpose of this paper is to summarize recent focus group data associated with AAW who indicated they received a mammogram in the past year. While effective communication is essential in achieving positive health outcomes for patients, studies have concluded that individuals from various culture groups deal with communication differently than do those from the dominant culture. The ultimate goal of this project was to document the experiences with receiving breast cancer messages using various technologies such as video-tapes, CD-ROMs, music-based CDs, Internet, and traditional educational methods to determine the impact of these technologies on health seeking behaviors. Two research questions guided the investigation 1) What technologies and experiences guide AA women in their decision making to seek mammography screening? and 2) Which technological strategy is most effective at increasing mammography use in AA women? Preliminary findings from the focus group study show that breast health messages are reaching African American women and AA women do have perceptions about which technology works best in motivating them to obtain mammography screening. Additional data show that AA women continue to experience barriers with these technologies, such as not being able to identify with the message, literacy levels, and convenience of receiving the message, all which still obstruct and delay participation in cancer screenings.

Hip Hop Food Pyramid - Obesity Prevention, Nutrition Education and Physical Activity Promotion Using Soul Music, NIH, SBIR Proposal 2010-00511

GGG-68

Translating evidence into practice in low resource settings: An experience of establishing a model Cancer Cervix screening programme in rural Tamilnadu, India – Rita Isaac

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Issues: Women in rural India have poor or no access to cervical cancer prevention and screening services, even though one–quarter of all cervical cancers in the world occur in India. Several large trials have proven the efficacy of low-tech cervical cancer screening methods in the Indian context but none have documented the necessary components and processes of implementing this evidence into a low-resource setting. There is an urgent need to establish affordable and acceptable cervical cancer screening programs for women in rural India.

Description: At RUHSA (Rural Unit for Health and Social Affairs) an outreach rural health programme of Christian Medical College, Vellore, Tamilnadu, India, we have established a model of Cancer Cervix screening programme for 20,000 women in the age group of 30 to 50 years residing in a rural development block. The programme introduced screening facilities using low-tech Visual Inspection of Cervix after Acetic acid application (VIA) as a screening tool in 18 sub-centres, trained public health nurses who provide routine outreach health care services as the primary screeners and peer educators within Self-Help women groups to raise awareness in the community. Of the 1173 women screened, 27 (2.3%) were VIA positive and all were referred to RUHSA Community Health Centre for further diagnostic work up. Five were treated with cryotherapy and five for reproductive tract infection only and remaining seventeen failed to keep their appointment for further testing.

Lessons learned: The experience revealed that the uptake of screening is low despite the easy access to a screening programme. However the programme witnessed an incremental increase in the number of women accessing screening with increasing awareness in the community.

Recommendations: The investigators recommend that making access to a cancer screening program should also focus on creating an environment and culture of screening as a preventive measure for cancer through education in low-resource settings.

GGG-69

Support for a community-based breast and cervical cancer prevention and control program in Dar es Salaam, Tanzania – Nedra Lisovicz

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The goal of this project was to conduct a feasibility study to determine if support exist for a community-based breast and cervical cancer prevention and control program in Dar es Salaam, Tanzania.
Objectives: 1). Conduct interviews and a focus group discussion with key leaders concerning existing health services and the capacity for breast and cervical cancer early detection and treatment. 2). Access support for implementation of a community-based health education program to promote early detection screenings for breast and cervical cancer. 3). Develop relationships between the study partners and Tanzanian leaders for future cancer prevention and control collaborations.

Methods: Data for this cross-sectional qualitative study were collected using the rapid appraisal method. Over forty key leaders completed semi-structured face-to-face interviews to discuss components needed for development of the community-based education program. Additionally the Community Health Management Team of Kinondoni District Municipal Council in Dar es Salaam participated in a focus group discussion concerning program development and implementation.

Results: The leaders overwhelmingly support development of a community-based health education program to promote survivor support and skills-building, including breast self-exam for early detection of breast cancer and preventive screenings for cervical cancer. As determined by information obtained from government leaders, the necessary political will exists to implement such a program. Reflecting the high disease burden and the low capacity for treatment, the leaders expressed the need to focus efforts on cervical cancer prevention and to increase capacity to accommodate enhanced demand for early detection and treatment of breast and cervical cancer.
Conclusions: There is strong support for development of collaboration between the study partners and Tanzanian leaders to develop a community-based pilot education program for breast and cervical cancer prevention and control. Next steps will include formative research to develop the initial program protocol.

Project support received from Rejoice and Hope Ministries International and the University of Alabama at Birmingham.

GGG-70

HPV and Cervical Cancer Screening, Prevention, and Treatment in Post-Crisis Reproductive Health Care Packages: A Needed Intervention for Refugee and Displaced Women – Jordann Loehr

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Human Papillomavirus (HPV) causes cervical cancer, the second leading cause of cancer deaths among women worldwide. Eighty percent of HPV cases occur in developing countries. Global health organizations have protocols to prevent healthcare gaps in crisis-affected populations. For example, the Minimal Initial Service Package (MISP) and the Comprehensive Reproductive Health (CRH) Services, found in the Sphere Handbook and endorsed by the United Nations Population Fund, (www.unfpa.org), the Reproductive Health Response in Crisis Consortium (www.rhrc.org), and numerous humanitarian organizations, provide protocols for implementing essential reproductive health care in crisis and post-crisis settings, respectively. These protocols have five key areas: inter-agency coordination, family planning, gender-based violence, maternal and newborn care, and prevention and treatment of sexually transmitted infections (STIs). Despite strong commitment of global health advocates to prevent HPV infections and screen for cervical cancer, neither the MISP nor the post-crisis CRH package include such measures in their protocols. This is a missed opportunity for early diagnosis and timely treatment of cervical cancer. Overall, preventive screening rates are low in developing countries and in women recently resettled from developing countries (Barnes and Harrison, 2004; Campbell et al., 2008). Oftentimes, those who become refugees are the least-served members of society, particularly in matters regarding reproductive health (McGinn, 2004). The CRH STI subject area involves syndromatic approaches to treatment of common STIs, STI surveillance testing, HIV testing, provision of necessary treatment, as well as STI education. This would be an ideal section in which to include pap smears, HPV testing, and other potential means of cervical cancer screening, prevention, treatment, and education. As occurs with the other MISP and CRH subject areas, we need vocal advocates to generate dialogue on including cervical cancer prevention and care in the Comprehensive Reproductive Health Services agenda for post-crisis populations.

GGG-71

Effects of Long-Term Use of Antiretroviral Therapy on the Prevalence of Oral Epstein-Barr Virus – Wipawee Nittayananta

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Epstein-Barr virus (EBV) can cause oral malignancy frequently observed in HIV-infected subjects before the wide use of antiretroviral therapy (ART). Previous studies reported that use of ART increased the prevalence of non-AIDS defining cancers of different organs. However, the effects of long-term use of ART on the risk of developing oral cancers are not well established. The purposes of this study were to determine 1) the prevalence of EBV in saliva of HIV-infected subjects compared to non-HIV controls, and 2) the effects of long-term use of ART on the prevalence of EBV in saliva of HIV-infected subjects. Quantitative real-time PCR was performed to detect EBV DNA in saliva of the following four groups; HIV-negative subjects (Group I: non-HIV controls, n=20), HIV-infected subjects who did not receive ART (Group II: no ART, n=13, mean CD4=206 cell/mm3), HIV-infected subjects receiving ART <3 years (Group III: short-term ART, n=17, mean CD4=251 cell/mm3), and HIV-infected subjects receiving ART ≥3 years (Group IV: long-term ART, n=19, mean CD4=525 cell/mm3). The copy number of EBV in saliva was found to be significantly higher in HIV-infected subjects than non-HIV controls (median=1766 vs. 0 copies/105 cells, p=0.0001). The copy number of EBV in saliva of HIV-infected subjects who were on ART was significantly lower than those who were not on ART (median= 388 vs. 162,636 copies/105 cells, p<0.0001). However, no significant difference was observed between those who received short-term and long-term ART (median= 1,221 vs. 418 copies/105 cells, p=0.23). Our results demonstrate that oral EBV was increased with HIV infection. The use of ART significantly decreased the number of EBV in saliva of HIV-infected subjects. Long-term use of ART did not seem to increase the prevalence of the virus.

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GGG-72

Cervical Cancer in Nigeria: The Case for Multidisciplinary Action – Folasade Odeniyi

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Globally, an estimated 500,000 cases of cervical cancer are diagnosed and over 288,000 deaths are recorded annually, with 80% of deaths occurring in developing countries (Nwankwo, 2011). In Nigeria, cervical cancer is the second leading cause of cancer death among women. Current estimates place the incidence at 20-30 cases per 100,000 people. In the United States, since the 1950s, the introduction of effective cancer control activities such as screening programs has led to a reduction in the incidence of cervical cancer from 38 to 5 cases per 100,000 people (Parkin 2008). The World Health Organization (WHO) advocates for effective cancer control to encompass four major components: primary prevention, early detection, diagnosis and treatment, and palliative care for advanced disease (WHO). Additionally, the hallmark of effective cancer control is the development of a comprehensive population-based cancer registry, as it provides reliable statistics for comparison of cancer risk between populations (Parkin 2008). While Nigeria has engaged in recent efforts to address the spectrum of non-communicable diseases, and cancer in particular, there is no formal cancer control plan, no standardized screening and early detection programs, and no nationally coordinated population-based cancer registries. Operation Stop Cervical Cancer in Nigeria (OSSCN), a multidisciplinary cross-collaboration among universities in the United States, Canada, and Nigeria, has established a cervical cancer screening program at six clinical sites across the country. Established in 2005, the initiative has aimed to foster collaboration in the development and diffusion of new detection technologies, knowledge sharing, infrastructure improvements, and the design of comprehensive cervical cancer control efforts to be replicated throughout the country and inform national cancer control strategies. As a result, to date, over 12,000 women have been screened. However, continued collaborations and financial support is necessary to ensure continued success of the program and replication throughout the country.

GGG-73

Improvement of palliative laser thermal therapy by identifying biomodulators that will impact outcomes – Marcos Paiva

Marcos B. Paiva, Michael Bublik, Joel Sercarz, Onivaldo Cervantes, Marcio Abrahao

BACKGROUND: Laser induced thermal therapy (LITT) has been developed in a step-wise phase I-II fashion at UCLA as a minimally invasive treatment for head and neck cancer (HNC). In two decades LITT has established in our institution mainly as a palliative treatment for recurrent tumors where 22% of patients remain free of disease after 5 years.

OBJECTIVE: To present our experience using LITT for palliation of 81 patients with recurrent HNC at the Cancer Detection and Diagnostics Technologies for Global Health as a starting point for discussion of possible biomodulators that can help identify patients with potential to benefit from adjuvant treatments such as chemotherapy (cisplatin), biologic therapy, radiation, etc. and improve tumor response and survival.

METHODS: eighty one patients with recurrent carcinoma of the head and neck were treated by LITT delivered by an Nd:YAG laser (energy densities = 2,200-3,300 J/cm2). Prognostic values were assessed using the Kaplan-Meier method.

RESULTS: Best results were seen in oral cavity tumors where mean survival was 29.1 months compared to neck (14.4 months, range: 7.5-20.7mo; 95%CI). The procedure was well tolerated in most of the 125 laser treatments (average 1.54 treatments/patient). Clinical factors as neck disease and tumor stage at first treatment were relevant prognostic factors.

CONCLUSION: LITT is a minimally invasive procedure that can be repeated as needed in palliative treatment of recurrent head and neck cancer. As a minimal invasive procedure usually done on an outpatient basis, LITT has the potential to be a low cost palliative treatment. However, identifying and testing biomodulators would significantly impact its use and expansion as an affordable more effective palliative treatment for cancer.

GGG-74

Biomarkers of gastric cancer and its precursors: potential to reduce gastric cancer mortality around the world – Lawrence Paszat

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Gastric cancer (GC) is a leading cause of cancer mortality among developing nations. The necessary cause for most cases is chronic infection by *Helicobacter.pylori*, which initiates and promotes GC precursors such as metaplasia and dysplasia in the gastric mucosa. Eradication of *H.pylori* moderately reduces the risk of carcinogenesis. Candidate biomarkers of the risk of serious precursors and invasive GC include the complex chronic host immune responses, *H.pylori* genes and their products, associated non-*H.pylori* microbiota, histology, and molecular markers of metaplasia, dysplasia, and carcinoma.

This work received ethics approval from the universities of Toronto and Gothenburg, and the Universidad Nacional Autonoma de Nicaragua—Managua. In 2010, we collected 30 ml of blood and 18 gastric mucosal biopsies from 140 consenting gastroscopy patients at a public teaching hospital in Managua, Nicaragua. Frozen blood, serum, and plasma were sent to Gothenburg, along with 8 frozen mucosal biopsies, including 2 in RNA-later and 2 in OCT cryomolds. 2 biopsies frozen in cystein medium were sent to Houston. In 2011 and 2012, we are collecting similar amounts of blood, and larger numbers of mucosal samples, from cases having gastrectomy for GC (average 1 per week). Reference histopathology is performed at the Unversity of Toronto and Universita di Padova.

The authors are determining the feasibility of developing biomarkers appropriate for detection of high-risk precursors and early GC in low-resource global settings, analyzing gastric and blood samples from series of gastroscopy and gastrectomy subjects in Managua, Nicaragua (high *H.pylori* prevalence, high GC mortality). The goal is to develop a method (based on biomarkers of gastric metaplasia, dysplasia and cancer) by which to identify a small group (< 5 %) of *H.pylori* infected adults from whom the majority of *H.pylori*-associated cases GC would emerge, feasible for use in low-resource, high-prevalence countries.

This work would be impossible without the enthusiastic participation of the patients at public hospitals in Managua, and the faculty and academic physicians and surgeons of the Universidad Nacional Autonoma de Nicaragua—Managua. Infrastructure, supplies, and funds to date have been provided by investigators at the University of Toronto, the University of Gothenburg, and Baylor College of Medicine.

GGG-75

BRCA1 and BRCA2 mutations in Mexican women with breast cancer – Catherine Phelan

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Among Latin American (LA) women, breast cancer is the most commonly diagnosed cancer and leading cause of cancer-related mortality. By the year 2050 Latinos will account for 25-30% of the total US population making them the largest minority population. Therefore reducing the burden of cancer in the US will depend on understanding cancer in this critical population group. We have established a network of breast cancer researchers from eight LA countries, (Breast cancer EtioLogy in Latin America (BELLA)) and have collected over 1880 breast cancer cases thus far, for the purpose of unraveling the genetic etiology of this disease in LA women. The prevalence of highly penetrant BRCA1/2 gene mutations in Latin American countries is largely unknown. We are screening the BRCA1 and BRCA2 genes in over 800 breast cancer cases from Mexico. In addition we have used ancestry informative markers to determine proportion of the three main ancestries; Amerindian, European or African in the women with breast cancer. Of the 21 mutations identifed so far, six are in BRCA1 and 16 are in BRCA2. Overall, the BRCA1 breast cancer cases have a mean age of 42.2 years whereas the mean age of the BRCA2 cases is 50.2 years. Our preliminary ancestry data suggests that the women with BRCA2 mutations have slightly higher African ancestry but lower Amerindian ancestry than the women with BRCA1 mutations. The spectrum of mutations in the BRCA1 and BRCA2 genes in Mexican women with breast cancer differs from published reports in Mexican American women (Weitzel et al, 2005) which may reflect increased admixture in the Mexican women living in the US and highlights the importance of genetic studies in women from native Latin American countries.

GGG-76

A New Method For Testing the Estrogen Receptor Status of Breast Cancers in Low Resource Countries – SuEllen Pommier

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Background: A collaborative team of OHSU and Myung Sung Christian Medical Center (MSCMC) physicians has been developed to serve the needs of patients in Addis Ababa, Ethiopia. Locally, breast cancer patients pursue treatment through non-medical means (e.g. cauterization). They present to Ethiopian surgeons with advanced breast cancer (BC), ulcerations, burns and scarring. Adjuvant chemotherapy which would improve survival is prohibitively expensive. Tamoxifen in contrast, is an inexpensive oral adjuvant treatment for estrogen receptor (ER) positive breast cancer. Since immunohistochemistry is lacking in low-resource countries, an alternative testing approach that determines the ER status of breast cancers is required in order to identify patients for whom tamoxifen treatment could significantly improve their survival. Methods: A simplified RT-PCR based diagnostic test was designed to determine the ER status of breast tumors. RNA /cDNA from ER-negative and positive samples was collected by spin column, and RT-PCR reactions containing primers for ER or GAPDH (internal control), fluorescent dyes, Taqman universal master mix and 100ng of cDNA (or water control) were performed. Amplified samples were visualized by SYBR green transillumination in a stationary gel matrix. To monitor reaction performance and assess correlation with gel matrix results, RT-PCR tests were performed on an Applied Biosystems 7900HT apparatus. Results: Three breast cancer cell lines, 8 ER positive or negative breast tumors and 3 normal breast tissue samples have been examined by RT- PCR. ER expression was significantly different between malignant and normal breast samples. RT-PCR results correlated with histochemical ER status. Thus, RT-PCR can discern ER-positive from negative tumors. Conclusions: The cost of this ER diagnostic test is currently $5.00. The equipment required is simple and long lasting. The results of this pilot study provide the foundation to further develop and evaluate this diagnostic tool in a site-appropriate program such as at the MSCMC in Ethiopia.

GGG-77

Knowledge and attitudes of HIV-infected and HIV-uninfected women regarding HPV and cervical cancer – Rajashri Rasal

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High-risk types of human papillomavirus (HPV), a sexually transmitted infection (STI), cause cervical cancer. Over 500,000 cases of cervical cancer are diagnosed each year, with 55% of them resulting in death. Education to increase awareness about prevention, early detection, and treatment, has helped reduced cervical cancer incidence and mortality among women in developed countries. Prevention of HPV-infection is particularly critical among HIV-infected (HIV+) women as they are more susceptible to infection by multiple types of HPV and other STIs compared to HIV-negative (HIV-) women. Health outcomes are also worse among HIV+ women. This pilot study assessed the baseline knowledge and attitudes regarding HPV and cervical cancer in HIV+ and HIV- women receiving outpatient primary care facilities in Philadelphia, PA. A cross-sectional self-administered survey was conducted among 70 HIV+ and 84 HIV- women. Overall, 62% were = 35 years old, 64% were non-Hispanic Black and 53% were single. More than 80% of the study participants had = 12 years of formal education, 35% were employed full-time and 48% had annual income below the poverty line. Most women (84% HIV+; 80% HIV-) reported having had a Pap smear within the last year. More than half (55%) of the HIV+ women reported that they had an abnormal Pap smear compared to 30% of HIV- women. HIV+ women were 3.3 times as likely to have had an abnormal Pap smear (p= 0.001). Only 19% of HIV+ and 14% of HIV- women received all three doses of the HPV vaccine. Knowledge about HPV infection, disease and prevention was low in both cohorts, but lower among HIV+ women (23% HIV+; 37% HIV-; p= 0.01). Such low knowledge levels regarding HPV infection, disease and prevention demands greater efforts to educate women on these issues. A larger comparative study is planned in the United States and in Nigeria.

GGG-78

Prostate Cancer Incidence and Survival Analysis and Trends – Anjali Shah

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Cancer is a major public health problem in United States (US) and many other parts of the world. Although progress has been made in reducing incidence and mortality rates and improving survival, cancer still accounts for one in four deaths in the US. Prostate cancer is among the leading causes of cancer deaths among men. In this paper, we examine prostate cancer rates by age, racial/ethnic group and income underlying the overall mortality trends of the disease within US. To study the mortality trends, we have compared age-adjusted mortality rates from Healthcare Cost and Utilization Project (HCUP)'s Nationwide Inpatient Sample (NIS) data among men by their race/ethnicity and economic status, and by their primary payer type of Medicare versus Non-Medicare. As a result of this analysis, outcomes analyzed show that Medicare patients have slightly better survivability rates (rate=98.57%) than patients prescribing to all other payer types (rate=98.19%) across all age groups, races and income groups for prostate cancer. Mortality rates show a prominent upward trend with increasing age groups. Patients in the lowest economic groups have highest mortality rates (3.53%) as compared to the other groups for the sample population across different payer types combined. We conclude that patient demographics and socioeconomic status plays a deterministic role in the estimated mortality rates for prostate cancer. Although, some of the results are not statistically significant, there is clearly indicative trend that supports the need for innovative research to eliminate disparities and improve survival rates across all patient segments.

GGG-79

Epidemiology and surgical management of breast cancer in Douala General Hospital – Charlotte Tchente Nguefack

Tchente Nguefack Charlotte[1], Essomba Biwole Martin[2], Massom Annie[3], Halle Gregory[1], Tsingaing Kamgaing Jacques[1], Nana Njamen Teophile[1], Egbe Thomas[1], Belley Priso Eugene[1]

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Summary Breast cancer is one of the common gynecological cancers in our milieu. Douala General Hospital (DGH) is the second center in Cameroon (the first one being at Yaound), where the cancerous patient can receive all aspects of their treatment. These are the only hospitals in the country where radiotherapy can be done. The aim of our study was to describe the epidemiological, clinical profile and surgical management of patient with breast cancer in DGH. A total of 42 patients were recruited in our department during a 3 years period (from November 2006 to October 2009). The mean age was 46 years (range: 29-73 years). Only 14.30% of patients were nulliparous. The main mode of discovering the disease was auto examination (91%). 3% of patients have family history of cancer; 2% of patients were recidivists of their first tumor. The clinical tumor size range from 2cm to 20cm with a mean of 6.83cm. Patients were then mostly diagnosed at stage III (31.70%) of the WHO classification. Ca15-3 was hardly increased even in patients with advanced tumor (2% of increase in the studied group). Neo adjuvant treatment was done in 80% of patients and the main surgical treatment was mastectomy (92.86%). Many patients are still followed up, but we already had a mortality rate of 14.29% at the end of December 2010. We lack feed back in some patients (26.19%). In conclusion, breast cancer is generally diagnosed in advance stage in our milieu; there is therefore a need of general sensitization and education of the population.

About 15 years after the first publications on breast cancer in our country: We still have a majority of cases diagnosed at late stages leading to radical surgery. It is obvious that there is need for health education, training and organization of campaigns for breast cancer screening We still have difficulties in getting good pathology results. Many prognostic factors are lacking: hormone receptors, Her2 neu etc. We really need to think about all this and improve, especially because women with breast cancer in our milieu are mostly young. Screening may start at 40 years instead of 50 in our milieu.

GGG-80

The Doctors Dilemma Anno 2011 – Huib Vriesendorp

Huib Vriesendorp[1] and Dirk Van Bekkum[2]

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In 1906 GB Shaw wrote the Doctors Dilemma, a play about ethical problems for doctors involved in clinical research. In a preface Shaw recommends his readers to have their mother find them a good doctor and let the Government pay for their health care. Two years later Paul Ehrlich accepted the Nobel Prize in Medicine for his discovery of the beneficial effects of arsenic salts in patients with syphilis and of Difteria toxin antisera. Ehrlich claims his success is based on 4Gs: in German Geld, Glueck, Geduld and Geschick. In English Money, Luck, Patience and Talent. He did not need another G for Gewin = Profit. His laboratory and operating costs were provided to him by Emperor Wilhelm II. In 2011 the Doctors Dilemma are caused by 5Gs. The Hippocratic Oath and its international derivative The Physician Charter advice doctors not to get involved in direct or indirect conflicts of interest in their patient care duties. CEOs of the Pharmaceutical Industry, Manufacturing Companies of diagnostic or therapeutic devices, University Hospitals, Health Insurance Companies are not bound by any medical ethics oath and aggressively pursue profits. They need doctors to perform clinical studies with their products. Doctors are advised to perform commercially driven clinical research rather than their own, financial less rewarding, investigator driven, clinical research. One of the reasons health care costs are rising to unsustainable levels. Cinderella identified promising drugs/devices abandoned by the Pharmaceutical/Manufacturing Industry due to lack of profit potential. Such drugs are step children like Cinderella and can be brought rapidly to patients in phase 2 studies, when doctors and institutions are willing to do such studies without making a profit. Cinderella will illustrate the potential of this approach by disclosing a new study of tumor reactive, radiolabeled IgM adminstered directly into solid tumor masses.

see www. Cinderella-tx.org

Poster Abstracts:

Molecular Analysis and Biomarker Research

MMM-81

Cyclotides, an ultrastable protein scaffolds for targeting protein/protein interactions – Julio A. Camarero

Julio A. Camarero, Ahmed E. Orabi, Yanbin Ji, and Krishnapa Jagadish

Department of Pharmacology and Pharmaceutical Sciences

Cyclotides have several characteristics that make them ideal drug development tools. First, they are remarkably stable due to the cystine knot. Second, they are small, making them readily accessible to chemical synthesis. Third, they can be encoded within standard cloning vectors, and expressed in bacteria or animal cells, and are amenable to substantial sequence variation. These characteristics make them ideal substrates for molecular evolution strategies to enable generation and selection of compounds with optimal binding and inhibitory characteristics. Finally, cyclotides have been shown to be orally bioavailable. For example, the first cyclotide to be discovered, Kalata B1, is an orally effective uterotonic , and other cyclotides have been shown to cross the cell membrane. Cyclotides thus appear as promising leads or frameworks for peptide drug design. We will be presenting our undergoing effort for the selection of novel cycotide sequences able to target protein/protein interactions involved in the p53 pathway.

This work was supported by National Institutes of Health Research Grant R01-GM090323 and Department of Defense Congressionally Directed Medical Research Program Grant PC09305.

MMM-82

Proteomic-based biosignature for breast cancer detection– From tissue proteomic analysis to blood test development – Helena Chang

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A highly sensitive and specific molecular-based blood test for breast cancer detection may transform cancer screening worldwide. Mass spectrometry (MS) was shown to be a powerful tool in discovering novel disease-related protein markers. However, direct detection of tumor markers in blood by MS has not been successful. We have designed a unique workflow to first study breast cancer proteomes by MS analysis in cancer cell lines and tissues followed by validation of the candidate markers in cancer using antibody detection methods. Combination of selected markers may guide the development of blood test for breast cancer detection.

We have investigated a panel of seven human breast cancer cell lines including 3 HER2 positive, 2 HER2 negative/hormone receptor positive (HER2-/HR+) and 2 triple negative (TNBC) cell lines. The secreted, sloughed or leaked proteins released by the cell lines into media were identified using nanoLC LTQ-Orbitrap. Of the 260 detected proteins, thromobospondin 1, galectin 3 binding protein, cathepsin D, CD44, EGFR, enolase1 and vitamin D binding protein were found in high abundance.

We then analyzed 59 breast cancer cases including 28 HER2+, 21 TNBC and 10 HER2-/HR+ breast cancer specimens using nanoLC LTQ-Orbitrap. We found that the breast cancer biomarkers detected in the proximal fluid were not only identified in cell lines but also in human specimens. The top twelve protein markers selected from the 59 breast cancer specimens include four extracelluar/secreted/trans-membrane proteins (enolase 1, vitamin D binding protein, annexin 2, and platelet derived endothelial cell growth factor 1) and eight cytoplasm/skeleton proteins (heat shock protein 70&90, annexin 5, L-plastin, peroxiredoxin 1, and cathepsin D). Some of these up-regulated proteins in invasive breast cancer may be used to develop a molecular-based blood test.

Grant support: the present study was supported by grant funds from NIH (NCI #1RO1 CA 093736-01A1), the Gonda Foundation, Entertainment Industry Foundation (EIF)/ Women's Cancer Research Fund, and Friends of the Breast Program at UCLA.

MMM-83

An integrated approach for biomarker identification in gastric cancer. – Juan Cui

Dr. Juan Cui

University of Georgia

We have developed an integrated approach for identification of potential biomarkers for gastric cancer in patients' cancer tissue, sera and urine, through combining genome-scale transcriptomic analyses on gastric cancer/reference tissues for identification of genes with differentially expressed patterns in gastric cancer tissues versus references, computational prediction of the differentially expressed gene products that may get secreted into blood or urine and experimental validation. By applying this approach to 80 pairs of gastric cancer and reference tissues, we have identified a number of highly promising gene markers in gastric cancer tissues and protein markers in serum and urine for gastric cancer. Overall, our study integrates computational and experimental approaches and takes full advantage of the information derived from omics data to guide the biomarker identification in serum and urine. The novel information obtained in this study has led to identification of very promising diagnostic markers in gastric cancer and can benefit further analyses of the key (early) abnormalities during its development.

MMM-84

Autofluorescence-Guided Diagnostics for Lesions of the Oropharynx – Jennifer Frustino

Jennifer L. Frustino, Vijayvel Jayaprakash, Maureen Sullivan, Mihai Merzianu, Nestor Rigual, Thom Loree, and Mary E. Reid

Background: Rates of cancer in the oropharynx (OP) are increasing therefore changes in screening and diagnosis are necessary. Adjuncts to clinical examination are critical in detecting lesions. Autofluorescence visualization (AFV) in addition to standard examination may become useful in the early detection of oral cancers (OC). Current screening tools are not always effective at examining the OP. We evaluated if the addition of AFV with white light exam (WLE) improved the ability to detect OP lesions using a 10mm rigid fluorescent endoscope for OP visualization and accessibility.

Methods: High-risk patients with suspicious lesions or recently diagnosed untreated OC /OP cancers underwent examination with WLE followed by AFV at 405nm from a 10mm rigid endoscope. Biopsies were obtained from areas with positive suspicion on either WLE or AFV examination. Lesions were stratified histopathologically and defined as low-grade (LGL), high-grade (HGL), or cancer. Sensitivity was calculated for WLE, AFV, and WLE + AFV for any patient with a biopsy from the oropharynx on the first visit. All biopsies were evaluated by the study pathologist.

Results: A total of 143 patients were seen and 664 biopsies were collected. From these, 29 patients had 41 biopsies taken from the OP or junction of the oral cavity/OP. Of the LGLs, 7 were parakeratosis with atypia and 13 were mild dysplasia. WLE alone vs. AFV alone vs. AFV+ WLE detected 35% vs. 85% vs. 95% of LGLs respectively. Of the HGLs, one was moderate dysplasia, 5 severe dysplasias and 6 carcinoma in situ. WLE alone vs. AFV alone vs. the addition of AFV+ WLE detected 75% vs. 100% vs. 100% of HGLs respectively. All 3 modalities equally detected the 2 cancers. Seven biopsies were benign. The addition of AFV+WLE provided greater sensitivity than WLE alone in detecting LGLs (95% vs. 35%) and HGLs (100% vs. 75%).

Conclusions: AFV may be a more sensitive tool to detect OP lesions that may have been missed by WLE.

MMM-85

Inflamed Leukocyte-mimetic Nanoparticles for Molecular Imaging of Inflammation and tumor microenvironment – Moonsoo Jin

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Dysregulated host inflammatory response causes many diseases, including cardiovascular and neurodegenerative diseases, cancer, and sepsis. Sensitive detection of the site of inflammation will, therefore, produce a wide-ranging impact on disease diagnosis and treatment. We hypothesized that nanoprobes designed to mimic the molecular interactions occurring between inflamed leukocytes and endothelium may possess selectivity toward diverse host inflammatory responses. To incorporate inflammation-sensitive molecular interactions, superparamagnetic iron oxide nanoparticles were conjugated with integrin lymphocyte function-associated antigen (LFA)-1 I domain, engineered to mimic activated leukocytes in physiology. Whole body optical and magnetic resonance imaging in vivo revealed that leukocyte-mimetic nanoparticles localized preferentially to the vasculature within and in the invasive front of the tumor, as well as to the site of acute inflammation. This study presents the first demonstration of in vivo detection of tumor-associated vasculature with systemically injected inflammation-specific nanoparticles, presenting a possibility of tumor detection by inflamed tumor microenvironment.

This work was supported by American Heart Association Scientist Development Grant and NIH R01 GM090320.

MMM-86

Squaramide-Based RGD Mimics A Potent Cell Adhesion Ligand for Functionalizing Multivalent Agents and Organic Microcapsules. – Yan-Yeung Luk

Sri Kamesh Narasimham, Deepali Prashar, and Yan-Yeung Luk

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We describe the use of a cyclic strained squaramide as a semi-rigid structural frame work to build a library of nonpeptide Arg-Gly-Asp (RGD) mimics. We discover that while this class of squaramides inhibits mammalian cell adhesion more potent than cyclic RGDs, when immobilized on a bioinert and density well-defined surfaces, they also induce more mature cell adhesion (smaller focal adhesion cluster and more fibrous stress fibers) than RGD ligands. We also describe tethering these squaramides on proteins to create multivalent agents with well-defined ligand spacing, and on a class of novel organic microcapsules as potential fluorescent reporters for cell over expressing adhesion proteins.

We thank Syracuse University, NSF-CMMI (# 0727491) for early and partial support for this work.

MMM-87

Biotinylated, Photoactivable Adenosine Analogs as Proteomic Profiling Tools – David Merkler

David Merkler

The identification of minor differences in proteomic profiles of normal and diseased biological samples can useful for the early diagnosis and development of new drugs to treat human diseases. One challenge is the design, synthesis, and implementation of reagents (or probes) that yield meaningful and reproducible proteomic profiles. Proteomic profiling probes based upon the adenine nucleosides and nucleotides (the AdoR's) would be particularly valuable given their metabolic centrality and role in cell signaling. Herein, we report on the synthesis and use of biotinylated, photoactivable adenosine analogs as binding-based proteomic probes. We first optimized the use of our AdoR probes against adenosine deaminase. Proteomic analysis by SDS-PAGE, Western Blotting, and LC-MS/MS resulted in an enrichment of ADoR probe-labeled proteins by affinity chromatography followed by identification and quantification of changes in concentrations of specific proteins obtained in comparing profiles between cancerous and non-cancerous human ovarian cells.

MMM-88

New Method for the Exclusive ?–Conjugation of Folic Acid – Judit Puskas

Judit E. Puskas

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Selectively delivering drugs to pathologic cells, thereby excluding the collateral damage that accompanies the drug intake by healthy cells is a very important objective. Efforts to reach this goal included searching for ligands that bind selectively to pathologic cells, but displaying very low or no affinity for healthy cells. After identifying an optimal targeting ligand, linkers that would carry the conjugated drug to the pathologic cells with receptors for the selected ligand need to be constructed. After the discovery of nondestructive folic acid (FA) receptor-mediated endocytosis on the upregulated folate receptor (FR) of certain mammalian cell lines, the targeted delivery of FA conjugated with BSA, ribonuclease, horseradish peroxidase, IgG, and ferritin was first reported in 1991. Since then, FA has been recognized as an effective targeting agent for cancer tissues including ovarian, lung, breast, kidney, brain, endometrial, colon, and hematopoietic cell cancers that overexpress folate receptor proteins (FRPs) bounded on the cell membrane. In contrast, in healthy cells FRPs are underexpressed . Thus, direct conjugation of virtually any desired drug molecule to FA is a good strategy for targeting cancer cells and facilitating high tumor cell specificity of FA-linked drugs.

Our group reports a new method (US Patent Application) for the exclusive ?-substitution of the glutamic acid moiety in folic acid. Folic acid was reacted with n-butyllithium, rendering the ?-position more reactive for subsequent conjugation. Specifically, the lithiated folic acid was reacted with bromo-alcohols, producing ?-substituted folic acid with an –OH group available for conjugation with other bioactive molecules.

MMM-89

Coupling Quantitative HPLC Profiling with In-depth MSn Disassembly for Comprehensive Structural Characterization of Neutral and Sialylated N-linked glycans – Vernon Reinhold

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An LTQ-Orbitrap mass spectrometry (MS) based approach for profiling and characterization of N-, and O-linked glycan pools comprising neutral and highly-sialylated glycan species has been developed. This approach efficiently links quantitative HPLC profiling together with capabilities for in-depth structural characterization by MSn disassembly. The profiling method employs established fluorescence labeling and detection methods, a charge-based HILIC HPLC (HIAX) separation, and online detection by negative ion Orbitrap-MS and LTQ MS/MS. Incorporating porous graphitized carbon (PGC) as a second chromatographic dimension, the workflow enables unimpeded mass spectrometry-based characterization by providing separation of the HIAX fractions, removal of buffer salts, and additional generation of positive ion Orbitrap-MS and LTQ MS/MS spectra. Low-abundance, unusual, or unexpected species requiring further characterization may be collected as buffer-free PGC eluant fractions for offline static nanospray (NSI) MS analysis where further aspects of detailed structure including identification of isomers, can be pursued via NSI-LTQ-MSn disassembly. Detailed aspects of topology including glycosidic linkages may be addressed following permethylation. The described workflow addresses both neutral and acidic glycans in a manner relevant to the needs of research settings where routine quantitative profiling needs to be efficiently coupled with capabilities for comprehensive structural characterization.

MMM-90

Metabolomics and Histology on the Exact Same Tissue Sample: Preservation by Extraction and Fixation – Dean Troyer

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Introduction and Objective: Histopathology is the standard method for diagnosis and histological grading and staging of cancer. One drawback to some molecular studies is that the portion of the tissue to be analyzed is processed in a manner that is destructive to the tissue. We present here a new method for performing analysis of small molecule biomarkers and histology in exactly the same biopsy tissue. The process, Molecular Preservation by Extraction and Fixation (MPREF), allows traditional histological examination to be combined with qualitative and quantitative analysis of small molecule biomarkers. METHODS 18 gauge core biopsies were obtained *ex vivo* from prostatectomy specimens. One core biopsy/specimen container was immersed in aqueous alcohol. After 12-24 hrs, biopsies were transferred to UMFIX, and the original alcohol retained. Histologic sections of biopsies were stained by routine methods and the immunohistochemical (IHC) stain, PIN4. Small molecular weight molecules in the retained alcohol were examined by a mass spectrometry-based method. RESULTS Light Microscopy: Tumor and grade were readily evaluable and IHC for PIN4 performed well. Metabolomics of Retained Alcohol: From a single core biopsy, 260 named biochemical compounds and their relative concentrations could be detected. 83 were different between the cancer and non-cancer biopsy extracts ($p < .05$). Eighteen of the 20 common amino acids, and a number of long chain fatty acids and phospholipids were increased. The highest fold changes, 4- to 6-fold, were observed with the compounds cysteine, dihomo-linoleate, docosapentaenoate, N acetylaspartate, N acetylglucosamine, uracil, xanthine, and 1 stearoylglycerophosphoinositol. A sub-set of candidate biomarkers were differentially expressed in pT3 vs pT2 disease. CONCLUSIONS The results suggest a higher metabolic state in cancer as compared with non-cancer containing biopsy tissues. Differential expression of small molecules from pT2 vs pT3 disease suggests that quantitative prognostic molecular and histologic data can be obatined from a single core biopsy.

The assistance of Tammy Wilson, Sentara Norfolk General Hospital Laboratory Services in preparing histological sections is acknowledged. The support of Sylvia Richendollar, VP Laboratory and Ancillary Services, and Virginia Hinson, Director, Anatomic Pathology Laboratory Services, Sentara Norfolk General Hospital, Norfolk, Virginia is gratefully acknowledged. The assistance of Elizabeth Smith, Biorepository Technician, Leroy T. Canoles Jr. Cancer Research Center, is gratefully acknowledged.

MMM-91

Fourier-transform Infrared Microspectroscopy Identifies Chronic Oxidative-Stress Associated Molecular Changes in Mammary Epithelium of Young Women: Insight into Early Latent Stage of Breast Carcinogenesis – Judith Weisz

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Background: Studies of cancers associated with certain occupations and with smoking provide evidence that it takes decades following exposure to initiating agent(s) for a cancer to emerge. Knowledge of changes during the decades-long latent phase of carcinogenesis is limited to when histological changes are already present because of a lack of biomarkers needed to identify in ostensibly normal tissues loci conducive to the evolution of cells that can initiate a cancer and by a lack of technologies for molecular-characterization of cells in such loci *in situ.*

Findings: Our findings, listed below, support the proposition that a marker of chronic oxidative-stress (OxS), protein-adducts of 4-hydroxy-2-nonenal (4HNE), identifies such loci in breast tissue sections and that synchrotron-radiation-based Fourier-transform infrared (SFT-IR) microspectroscopy can provide a molecular profile of cells present in such loci.

1) Foci of 4HNE-immunopositive (4HNE+) mammary epithelial (ME) cells are prevalent in reduction mammoplasty tissues of women and even in that of teenagers representative of USA's high BC-incidence population:

2) Tissues with many 4HNE+ ME cells vs. those with few 4HNE+ cells differ markedly in the expression of genes associated with OxS:

3) Differences in biomolecular signature of cells within 4HNE+ vs. 4HNE- terminal lobular ductal units (TDLUs) identified by SFT-IR microspectroscopy in tissues from women ages 20-25 yr. Specifically, infrared spectra subjected to principal-component and linear-discriminant analyses revealed differences ($P < 0.0001$) between 4HNE+ vs. 4HNE- TDLUs associated with DNA alterations, notably, symmetric phosphate-stretching vibrations (v_sPO_2-). Comparison of luminal vs. myoepithelial cells highlighted the presence of cells-distinguishing markers of stem cell-associated v_sPO_2- (1080 cm-1) that segregated from the rest of the epithelium.

Conclusions: The findings support the hypothesis that many environmental/lifestyle factors implicated in cancers associated with "westernization" contribute to carcinogenesis by contributing to OxS, a hypothesis that is testable using new tools of molecular pathology, such as ST-FTIR.

Rosemere Cancer Foundation (FM), The Pennsylvania State Tobacco Settlement Formula Fund (JW) and Pennsylvania Breast Cancer Coalition (JW)

MMM-92

Imaging Bread Cancer Metastasis by u-SPECT/CT with Tc-99m-3P-RGD2–Yang Zhou

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Breast cancer is the second leading cause of deaths among women worldwide. Metastatic breast cancer is characterized by spreading of cancer cells into nearby breast tissue, and other body parts (bone, lymph nodes, liver and lungs). During metastasis, breast tumor cells attach to extracellular matrix proteins, release proteases that degrade the basement membrane, and invade through degraded basement membrane to spread to other body parts through circulation. It has been reported that integrin αvβ3 plays a significant role in progression of invasive breast cancer. The integrin αvβ3 activation is required for hematogenous breast cancer metastasis. Integrin αvβ3 is an important prognostic biomarker for highly invasive breast tumors. 99mTc-3P-RGD2 is a new radiotracer specific for the integrin αvβ3 overexpressed on breast cancer cells and tumor neovasculature. Previous studies showed that 99mTc-3P-RGD2 is useful for early-detection of integrin αvβ3-positive tumors in xenografted animal models. To further expand its diagnostic utility, we established two breast cancer metastasis models, and used a u-SPECT/CT scanner to image breast cancer metastases with 99mTc-3P-RGD2 as the radiotracer. Our imaging data clearly showed that breast cancer metastasis lesions in lungs, mandible, maxilla, spinal cord, rib, neck and lymph nodes in the underarms could be readily detected. Histological staining studies further confirmed the existence of most tumors. The smallest lesion detectable by u-SPECT/CT is ~2 mm in diameter. Larger breast tumor tissues (>0.2 g) were quite heterogeneous with respect to the radiotracer uptake and integrin αvβ3 expression levels due to the presence of necrosis. In necrotic area of the tumor tissue, there was very low integrin αvβ3 expression, leading to low uptake of 99mTc-3P-RGD2. Our imaging data clearly showed that each animal had its own distinctive metastasis patterns. 99mTc-3P-RGD2 is an excellent radiotracer for detection of breast cancer metastasis to bone and lungs.

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MMM-93

Elevated expression of squamous cell carcinoma antigen (SCCA) is associated with human breast carcinoma – Wei-Xing Zong

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Squamous cell carcinoma antigen (SCCA) belongs to the serine protease inhibitor (Serpin) family of proteins. Elevated expression of SCCA has been used as a biomarker for aggressive squamous cell carcinoma (SCC) in cancers of the cervix, lung, head and neck, and liver. However, SCCA expression in breast cancer has not been investigated. Immunohistochemical analysis of SCCA expression was performed on tissue microarrays containing breast tumor tissues (n=1,360) and normal breast epithelium (n=124). SCCA expression was scored on a tiered scale (0-3) independently by two evaluators blind to the patients clinical status. SCCA expression was observed in Grade I (0.3%), Grade II (2.5%), and Grade III (9.4%) breast cancers ($p<0.0001$). Comparing tissues categorized into the three non-metastatic TNM stages, I-III, SCCA positivity was seen in 2.4% of Stage I cancers, 3.1% of Stage II cancers, and 8.6% of Stage III breast cancers ($p=0.0005$). No positive staining was observed in normal/non-neoplastic breast tissue (0 out of 124). SCCA expression also correlated to estrogen receptor/progesterone receptor (ER/PR) double-negative tumors ($p=0.0009$). Compared to SCCA-negative patients, SCCA-positive patients had both a worse overall survival and recurrence-free survival ($p<0.0001$ and $p<0.0001$, respectively). This study shows that SCCA is associated with both advanced stage and high grade human breast carcinoma, and suggests the necessity to further explore the role of SCCA in breast cancer development and treatment.

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BBB-94

Detection of melanoma by non-invasive volatile metabolomic approach – Tatjana Abaffy

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The quest for melanoma biomarkers is paramount. There is a need for reliable biomarkers that would help in the diagnosis of this aggressive disease. Our goal is to identify melanoma volatile biomarkers using a non-invasive approach. In order to detect volatile metabolic signature of malignant melanoma, we are using a modified Head Space Solid Phase Micro-Extraction Method (HS-SPME) and Gas Chromatography/Mass Spectrometry (GC/MS). This method uses a sorbent-coated tape to extract compounds for their subsequent desorption into the gas chromatograph. We are enrolling melanoma patients at early stage of the disease (in situ, stage I and stage II). The volatile metabolome exhibits significant natural variation and it may be very hard to find a variation caused by disease. To overcome this limitation, as a control, we are using perfectly matched, non-neoplastic, un-involved skin tissue from the same patient. Our novel approach to detect and identify volatile metabolites released from melanoma tissue will be compared with a volatile analysis from the tissue obtained by biopsy. Early diagnosis of melanoma by a non-invasive method based on the specific pattern of volatile biomarkers is a novel and promising approach that would enable future studies on much larger groups to separate diagnostic, prognostic and predictive biomarkers.

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BBB-95

Carcinoma Matrix Controls Resistance to Cisplatin through Talin Regulation of NF-kB – Allison Berrier

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The extracellular matrix factors within the tumor microenvironment that control resistance to chemotherapeutics are poorly understood. Our studies focus on understanding matrix factors and adhesion pathways that control the oral carcinoma response to cisplatin since nearly 80% of oral carcinomas are resistant or develop resistance to cisplatin during therapy. Our studies reveal that adhesion of oral carcinoma lines HN12 and JHU012 to carcinoma matrix mediates tumor cell proliferation in response to treatment with cisplatin. Similar proliferation was not observed in HN12 cells adherent to other purified extracellular matrices such as Matrigel, collagen I, fibronectin or laminin I. Integrin β1 was important for adhesion to carcinoma matrix to trigger proliferation after treatment with cisplatin. Disruption of talin expression in HN12 cells adherent to carcinoma matrix increased cisplatin induced proliferation. Pharmacological inhibitors were used to determine signaling events required for talin deficiency to regulate cisplatin induced proliferation. Pharmacological inhibition of NF-kB reduced proliferation of talin-deficient HN12 cells treated with 30 μM cisplatin. Nuclear NF-kB activity was assayed in HN12 cells using a luciferase reporter for NF-kB transcriptional activity. Nuclear NF-kB activity was similar in HN12 cells adherent to carcinoma matrix and collagen I when treated with vehicle DMSO. Following treatment with 30 μM cisplatin, NF-kB activity is maintained in cells adherent to carcinoma matrix whereas NF-kB activity is reduced in collagen I adherent cells. Talin overexpression triggers proliferation of HN12 cells adherent to collagen I following treatment with 1 and 30 μM cisplatin. Talin overexpression was sufficient to trigger NF-kB activity following treatment with cisplatin in carcinoma matrix adherent HN12 cells in a process disrupted by FAK siRNA. Thus, the carcinoma matrix is a microenvironment in which exposure to cisplatin induces tumor cell proliferation through the function of integrin β1, talin and FAK pathways that regulate NF-kB nuclear activity.

We thank the Department of Oral and Craniofacial Biology for use of core facilities and T. Foster for a luminometer. We thank A Huttenlocher and WK Song for providing the Talin and Cas constructs. We thank KM Yamada and H Kleinman for matrix proteins and insightful comments. We thank the LSUHSC-NO SOD for their financial support.

BBB-96

Aristolochic Acid Nephropathy: An Environmental and Iatrogenic Disease – Kate Dickman

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Endemic (Balkan) nephropathy (EN) is a chronic kidney disease that is highly associated with urothelial cell carcinomas (UUC) of the upper urinary tract. We have linked both disorders to environmental exposure to aristolochic acid (AA), a potent nephrotoxin and human carcinogen produced by *Aristolochia* plants that grow in wheat fields in endemic sites and contaminate the flour used to prepare bread. Based on the use of *Aristolochia* in traditional herbal medicines, particularly in Asia, we posited that aristolochic acid nephropathy (AAN) represents a long-overlooked iatrogenic disease and an international public health problem of considerable magnitude (*Adv Mol Tox* 3, 211, 2010). Pursuing this hypothesis, we conducted studies of patients with UUC residing in Taiwan, or in regions of Croatia, Bosnia and Serbia where EN is prevalent. DNA was obtained, with informed consent, from renal cortical and tumor tissues following nephroureterectomy. AA reacts with DNA to form aristolactam (AL)-DNA (AL-DNA) adducts that serve as highly specific biomarkers of internal exposure to AA. These lesions lead to unique hotspots of mutagenic A:T transversions in the tumor suppressor gene TP53, providing a biomarker of effect. AL- DNA adducts, measured by ^{32}P- post-labeling techniques, were detected in the majority of patients with UUC from Taiwan (25/45, 56%) and EN regions (47/67, 70%). Chip-sequencing technology showed that the TP53 mutation spectrum was dominated by A:T->T:A transversions located almost exclusively on the non-transcribed DNA strand, reflecting a failure to excise AL-DNA adducts by global genomic nucleotide excision repair. This factor may account for the remarkable persistence of these adducts in human tissues. Thus, AA joins aflatoxin and vinyl chloride as one the few human carcinogens with a definitive TP53 mutational signature. The AA mutational signature, in conjunction with the presence of AL-DNA adducts as biomarkers of exposure, establishes an etiological role for AA in UUC. Public health authorities in countries where *Aristolochia* has been used are encouraged to initiate screening programs to detect UUC and to implement measures that will reduce human exposure to this nephrotoxic and carcinogenic herb.

(Supported by NIEHS).

BBB-97

Noncoding RNA signature for triple negative breast cancer – Suranganie Dharmawardhane

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Of the 1 million cases of breast cancer diagnosed annually worldwide, over 170,000 is estimated to harbor the triple negative (estrogen receptor (ER)/progesterone receptor (PR)/Her2 (neu, erbB2) negative) phenotype. Triple negative breast cancer (TNBC) disproportionately affects pre-menopausal women as well as African American and Hispanic women. TNBC incidence is rising in Puerto Rico where most women are of Spanish, African, and native Taino descent. This aggressive type of breast cancer is associated with poor overall patient prognosis due to limited treatment options, since ER, PR, and Her2 are usually targeted in successful breast cancer therapy. Therefore, it is critical to understand the molecular mechanisms by which receptor expression is lost during progression to TNBC. To elucidate a mechanism for ER, PR, and Her-2 loss in TNBC, we are investigating a class of recently identified molecules called noncoding RNAs (ncRNAs) that include microRNAs (miRNA), the most abundant short non-coding transcriptional or post-transcriptional regulators. ncRNAs have been implicated in cancer as both tumor suppressors and oncogenes through imperfect pairing and subsequent degradation of target mRNAs of genes coding for proteins that regulate cancer. Our objective is to conduct a large scale study to identify the ncRNAs of tumor tissues from breast cancer patients with ER (+), PR (+), Her-2 (+) status; ER (-), PR (-), Her-2 (+) status; and ER (-), PR (-), Her-2 (-) status to identify ncRNAs that differentially regulate each breast cancer subtype. Data will be presented from tumor tissue of TNBC and non-TNBC that show up- or down-regulation of specific miRNAs associated with ER/PR/Her2 expression. Since we can measure circulating miRNAs in serum and plasma, we hope to ultimately utilize this knowledge to identify circulating ncRNAs as noninvasive TNBC biomarkers from body fluids of women at high risk.

This study was supported by NCRR/NIH 2G12RR003035-25 to UCC and NIGMS/NIH GM084824 to SD.

BBB-98

Effective design and statistical analysis of cancer detection and diagnosis protocols – Jimmy Efird

Jimmy T. Efird

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This talk will address how to clearly define study endpoints, randomly select balanced block sizes in a multisite study and optimize power/study design using correlated sampling methods. An overview of robust statistical methods for analyzing cancer detection/diagnosis studies, such as likelihood ratio classification, will be provided.

BBB-99

Methylation portraits from the front-lines: Towards a world-wide network for cancer early detection and diagnosis research in low-income countries – Rafael Guerrero-Preston

Rafael Guerrero-Preston[1], Ethan Soudry[1], Kim Ostrow1, Priscilla Brebi[2], Carmen Ili[2], Martha Jahuira[3], Manuel Bayona[4], Hernn Vargas[5], Carlos Golijow[6], Robert Gilman[3], Juan Roa[2], Jaime Matta[7], and David Sidransky[1]

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Differential DNA methylation alterations are optimal indicators for carcinogenic risk estimation, prognostication, and therapeutic development - basic elements needed in a platform for personalized medicine, cancer prevention and health promotion efforts. However, most methylation studies have been conducted on patients treated in North America and Europe using very costly equipment, which limits their usefulness in low-income countries. We identified the need to develop a network for cancer early detection and diagnosis research in low-income countries. Using our previous experience in the National Cancer Institute Early Detection Research Network we partnered with laboratories in Puerto Rico, Chile, Per, Colombia, and Argentina to use low cost early detection and diagnostic tools, in combination with high throughput discovery tools provided by our laboratory in USA. Using Methylation Specific PCR (MSP) we identified two hypermethylated genes, ZNF516 and GGTLA4, as biomarkers for early detection in cervical cancer in a project with our colleagues from Chile. Using an Elisa based technique we found that a global DNA methylation index can significantly distinguish (p-value <0.0001) between gastric cancer cases (mean = 3.7; 95% CI, 2.99, 4.39) and controls, (mean = 5.7; 95% CI, 4.94, 6.34), as well as between superficial (mean = 6.4; 95% CI, 5.34, 7.50) and deep inflammation (mean = 4.7; 95% CI, 3.74, 5.56) in a case-control study from Per. Using quantitative MSP(qMSP) we identified three genes as potential early detection breast cancer biomarkers in serum DNA from a breast cancer case-control study in Puerto Rico. The Receiver Characteristic Operator Curves (ROC) for individual genes revealed area under the curve values of at least 0.71: MAL (0.84), KIF1a (0.71), OGDHL (0.33). The proposed network of early detection and research laboratories we are establishing in Latin America can be a useful model to establish similar networks in Asia and Africa.

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BBB-100

Comprehensive strategy for autoantibody-based analysis of cancer – Tomasz Heyduk

Ewa Heyduk, Agnieszka Lass-Napiorkowska, and Tomasz Heyduk

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Molecular biomarkers hold a great and yet unfulfilled promise as convenient, inexpensive and noninvasive tools for cancer analysis and detection. Currently available molecular biomarkers exhibit disappointing performance in terms of sensitivity and specificity. Autoantibodies produced by patients immune system in response to cancer are emerging alternative biomarkers with great potential to achieve clinically applicable specificity and sensitivity. We describe a novel comprehensive integrated strategy, which combines discovery of reagents (short peptides) specific for cancer autoantibodies with a straightforward assay platform that can readily utilize these reagents for multiplexed autoantibody detection. Ribosome Display (RD) in vitro selection is used to isolate from high complexity random sequence peptide library peptide reagents that could bind to the autoantibodies with high specificity. These peptide reagents can be subsequently used to prepare peptide based assays that allow homogenous mix-and-read format detection of antibodies with pM limits of detection and high specificity.

BBB-101

Electrical Properties of Cells on NanoStructured Thin Film Surfaces: An Approach towards Detection of Rare Tumor Cells – Balaji Panchapakesan

Balaji Panchapakesan[1] and Eric Wickstrom[2]

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The electrical properties of different types of cells on nanostructured surfaces has not been explored in detail. Exploration of unique signatures of different types of cells can have impact in diagnostics based on small volume of blood. In this presentation, we show the different levels of change in electrical signatures of blood, isolated white blood cells, breast cancer cells and blood mixed with breast cancer cells. These unique signatures enable the detection of small number of breast cancer cells mixed in blood with out fouling. Further, this fundamental study can impact wide variety of diagnostics based on blood samples.

NSF CAREER AWARD: 0853066

BBB-102

IR Spectroscopy for automated low cost molecular diagnosis of cancer – Kenneth Puzey

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IR spectroscopy of breast tissue biopsies was used to differentiate cancerous and normal tissue. In addition, ER+ and ER- negative breast tissue was differentiable with IR spectroscopy. Further, HER2/neu overamplified and HER2/neu mormal breast tissue were differentiable by IR spectroscopy. It appears that IR spectroscopy has promise as an automated high throughput diagnostic method that is inexpensive, sensitive, and specific.

Funding for this project was provided by Vermont EPSCOR

BBB-103

Evaluation of strategies for optimal clinical management of women with atypical squamous cells of undetermined significance (ASCUS): Design and Pilot phase. – Gloria Sanchez

Sánchez GI[1], Almonte M[2], Baena A[1,3], Bedoya AM[1,3], Cuello L[1], Villa C1, Botero MA[1], Zapata AM[1],Borrero M[1,4], Córdoba CM[1,4], Rojas F[5], Pareja R[5], Buitrago C[6], Gómez LJ[7], Londoño LH[8], Ortiz N[9], González M[9], and Herrero R[10]

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Introduction: The immediate colposcopy or cytology at 6 or 12 months is the current scheme for the management of ASCUS cytology of women in Colombia. HPV testing is superior to cytology for detection of cervical high grade lesions and studies show that strategies that include HPV test may represent a more favorable and cost-effective alternative than current strategies.

Objective: To compare the effectiveness of three strategies (1. triage with cytology followed by colposcopy if abnormal cytology at six and / or twelve months 2. immediate colposcopy, and 3. triage with HPV testing followed by colposcopy in HPV-positive) for the management of women with ASCUS cytology in clinical settings of Medellin, Colombia, to reduce the prevalence of intraepithelial neoplasia grade two or more severe lesions (CIN2 +) after two years of follow-up.

Methods: A Randomized, Parallel Arm, Comparative, Non-blind study. 2868 women with ASCUS Pap results (according to the laboratories of the health service providers) are being recruited via community cytology labs by telephone calls and randomized in a 1:1:1 ratio to receive Pap at 6 and/or 12 months (CITO), immediate Colposcopy (COLP) or HPV test (HPV). All women with positive test (ASCUS+ or HPV+) are immediately referred to colposcopy with their respective service providers. All participants will attend follow-up visits at 12 and 24 months after study entry. At 12 months, women with High grade SIL cytology will be referred to colposcopy. At 24 months, all women will receive an HPV test and if positive will receive colposcopy by gynecologists of the study. Women diagnosed with CIN2+ are treated with electro-surgical loop (LEEP) or clinical management if necessary through their respective service providers. The main outcome of the study is the prevalence of CIN2 + lesions in each of the arms after the follow-up visits (two years of entry to the study). Other secondary outcomes to be evaluated are: i) referral rates for colposcopy on each arm, ii) the acceptability of HPV testing for ASCU S Pap women, iii) the acceptability of the HPV test by medical specialists for the evaluation and treatment of women with ASCUS cytology, iv) the efficiency of access to health services according to the strategies v) the cost-effectiveness of each strategy.

Advances in the study: collaboration agreements were established with 4 health care organization and 4 health care institutions that jointly provide services to 60% of the population of Medellin. The study was approved by the Ethics Committee of the University of Antioquia and the participating institutions. Methods for collecting and managing data according to Good Clinical Practices have been implemented. Up-today 350 women have been recruited. Preliminary data shows 60% recruitment success and that balance between arms have been achieved. Data on referral rate at entry will be presented at the meeting.

BBB-104

New Panel of Predictive Biomarkers for Metastatic Colorectal Cancer Patients Stratification – Elena Schwartz

Schwartz Elena, Ph.D., Ekaterina Kotelnikova Ph.D., Maria Sahkrob Ph.D., Mikhail Pyatnickiy Ph.D., and Nikolai Daraselia Ph.D.

Ariadne, 9430 Key West Rd, Rockville, MD 20850

Introduction: Cetuximab (Erbitux®) and panitumumab (Vectibix®) are monoclonal antibodies that bind to EGFR. These drugs are approved by the FDA for the treatment of metastatic colorectal cancer (mCRC) patients. Currently, KRAS mutation testing is recommended before starting EGFR-targeted therapy in mCRC patients. About 60% of mCRC patients have the wild-type (WT) KRAS sequence and are therefore eligible for anti-EGFR therapy. Unfortunately, most of these patients (55-60%) do not respond to this treatment and consequently do not obtain clinical benefits from this therapy. The study goal was to identify a panel of prognostic biomarkers using a combinatory approach that can be used for screening mCRC patients (WT KRAS) in order to identify non-responders to anti-EGFR treatment.

Methods: The Sub-Network Enrichment Analysis (SNEA) approach developed by Ariadne was used to analyze datasets that included 703 CRC and 79 matching normal cases. Based on this approach, individual expression profiles of patients were compared to normal and then SNEA was employed to find significant regulators (173). These regulators were grouped into 14 pathways using the functional network. Next, we compared the gene expression profiles of mCRC patients who responded to anti-EGFR treatment to patients with no response by using the same approach.

Results: Fifteen potential biomarkers have been pre-selected for mCRC patients that can distinguish responders to anti-EGFR therapy from non-responders. Non-responders had an activated TGFβ pathway out of 14 pathways defining major sub-types of 703 CRC patients.

Discussion: These 15 candidates will be validated using a set of colorectal cells with WT KRAS. Once validated, the panel could be developed into a variety of assay platforms, some of which may serve global health goals.

BBB-105

Gas Biomarkers From Leukocytes: Non-Invasive Disease Detection of Hematopoietic Malignancy – Hye-Won Shin

Hye-Won Shin[1,2], Brandon Umber[3], Michael Lilly[4], Frank P. Zaldivar[1,2], Szu-Yun Leu[1,2], Pierre Baldi[5], Donald R. Blake[3], and Dan. M. Cooper[1,2]

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The overall objective of this study is to identify volatile organic compounds (VOCs) released from malignant leukocytes that ultimately can be detected in human breath as non-invasive biomarkers for hematopoietic malignancy. We hypothesized that malignant leukocytes could generate malignancy type-specific gasses which are distinct from normal leukocytes. To test the hypothesis, we draw on our current interdisciplinary collaboration among biomedical engineers, chemists, clinical oncologists, respiratory physiologists, and biostatisticians to design studies to identify trace gases obtained in vivo from the exhaled breath of hematopoietic malignancy patients and in vitro cultured leukocyte cells. A bioreactor coupled with a multi-column/detector gas chromatography system that was designed and built for this specific purpose will be used (J Transl Med. 2009 7:31). This system is capable of quantifying biological trace gases from cells in culture and from human exhalant in the concentration range of parts per billion to parts per trillion. Our study demonstrated that unique VOCs were observed from hematopoietic malignancy patients exhaled breath and malignant leukocyte cells in culture obtained from patients. For example, 2-pentanone was highly elevated from both headspace above the isolated leukemia cells in culture and exhaled breath of leukemia patients. In addition, an acute myeloid leukemia patient has higher levels of 1-propanol in the exhaled breath compared to the healthy controls in the same room. Interestingly, this peak disappeared following treatments. If malignant leukocytes produce measureable VOC biomarkers, present in the exhaled breath of hematopoietic malignancy patients with high sensitivity and specificity, then it is hoped that this new methodology may provide a non-invasive compliment and/or enhancement to established hematopoietic cancer diagnostics. In addition, detected VOCs may indicate the presence of new metabolic pathways and cellular biology, which may guide future therapeutic treatment options for hematopoietic cancers.

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BBB-106

A Non-Invasive Method of Brain Tumor Detection: Urinary Biomarkers Predict Brain Tumor Presence and Response to Therapy – Edward Smith

Edward Smith

Department of Neurosurgery and Vascular Biology Program, Children's Hospital Boston, Harvard Medical School, Boston, MA

Introduction: A major difficulty in treating brain tumors is the lack of effective methods of identifying novel or recurrent disease. In this study, we have evaluated the efficacy of urinary matrix metalloproteinases (MMPs) and associated molecules as diagnostic biomarkers for brain tumors. Methods Urine, cerebrospinal fluid and tissue specimens were collected from patients with brain tumors. Zymography, ELISA and immunohistochemistry were used to characterize the presence of MMP-2, MMP-9, MMP-9/NGAL and VEGF. Results were compared to age and sex-matched controls and subjected to statistical analyses. Results Evaluation of a specific panel of urinary biomarkers by ELISA demonstrated significant elevations of MMP-2, MMP-9, MMP-9/NGAL and VEGF (all $P < 0.001$) in samples from brain tumor patients compared to controls. Multiplexing MMP-2 and VEGF provided superior accuracy compared to any other combination or individual biomarker. ROC curves for MMP-2 and VEGF showed excellent discrimination. Immunohistochemistry identified these same proteins in the source tumor tissue. A subset of patients with longitudinal follow-up revealed subsequent clearing of biomarkers following tumor resection. Conclusions We report, for the first time, identification of a panel of urinary biomarkers that predicts the presence of brain tumors. These biomarkers correlate with presence of disease, decrease with treatment and can be tracked from source tissue to urine. These data support the hypothesis that urinary MMPs and associated proteins are useful predictors of the presence of brain tumors and may provide a basis for a novel, non-invasive method to identify new brain tumors and monitor known tumors following treatment.

Dr. Marsha Moses and the Fellows Brain Tumor Research Fund and the Emma Marrone Brain Tumor Research Fund, the American Brain Tumor Association

BBB-107

Amide proton transfer MRI signal as a novel imaging biomarker for assessing radiation necrosis in the rat brain – Silun Wang

Silun Wang[1], Erik Tryggestad[2], Tingting Zhou[1], Michael Armour[2], Zhibo Wen1, Eric Ford[2], De-Xue Fu[3], Peter C.M. van Zijl[1,4], and Jinyuan Zhou[1,4]

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Propose: We propose to explore the imaging features of radiation induced delayed brain necrosis in a pre-clinical animal model using amide proton transfer (APT) imaging with unique magnetic resonance imaging (MRI) contrast based on endogenous mobile proteins and peptides. Methods and Materials: Eighteen adult rats (Fischer 344, 200-250 g) were irradiated with a 10 mm2 region on the left×single, well-collimated X-ray of 40 Gy to a 10 hemisphere. Multiparametric MRI was performed on 25 1 weeks post-radiation until radiation necrosis was observed. Imaging signal intensities were analyzed on radiation necrotic core, peri-necrotic region and contralateral normal brain on APT images and compared the results with those obtained by T1, T2, magnetization transfer ratio (MTR), apparent diffusion coefficient (ADC) and cerebral blood flow (CBF). The imaging results were validated by H&E staining. Results: Radiation necrosis was hypointense on necrotic cores and iso-intense or slightly hyperintense on peri-necrotic regions on the APT images. Signal intensities of APT image were significantly lower in radiation necrotic core than those of the 0.99% vs. -2.13±normal brain (-3.49% 0.76%, p± < 0.01), whereas similar APT signal intensities were found between peri-necrotic region and the normal 0.76%, p± 1.19% vs. -2.13 ±brain (-1.44% > 0.05). Radiation necrotic core and peri-necrotic region on APT images corresponded to fibrinoid necrosis and reactive astrogliosis or vascular damage, respectively. Other MRI techniques could not detect significant differences between necrotic core and normal brain (T1, T2, MTR and ADC) or had limited signal-to-noise ratio (CBF). Conclusions: APT imaging showed unique imaging features of radiation necrosis. Quantitative analysis of APT signal intensities provides useful information to characterize the radiation necrosis.

This work was supported in part by grants from NIH (EB009112 and EB009731) and the Dana Foundation.

BBB-108

Mucin 5B may be a Specific Indicator of Mucinous Pancreatic Cysts – Anthony Yeung

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CEA is currently the best indicator correlating with a pancreatic cyst being mucinous (Brugge, Gastroenterology. 2004 126:1330-6). Mucinous cysts are often cancerous. We performed proteomic analysis of pancreatic cyst fluids obtained by EUS-FNA and found that there are several forms of mucins in the cyst fluids including mucin 5AC and mucin 5B (Pancreas, 38:e33-e42, 2009). Only one microliter of cyst fluid is necessary for this assay to be done by mass spectrometry, providing hope for earlier determination of whether a small cyst, or one with little fluid, may be mucinous, and candidate for early intervention. Mucin 5AC is the most abundant, but can be present because of stomach contamination when the FNA needle passes through the stomach wall. It is known in literature that mucin 5B mRNA has never been found in the normal stomach mucosa and the protein was not found by immunohistochemistry. Therefore we propose that mucin 5B may be a specific indicator of mucinous pancreatic cyst with the potential to replace CEA for this indication.

This study was supported by the National Cancer Institute, CA119242 and P30CA06927, the Ewing Trust, the Driskill Foundation, the Fannie E. Rippel Foundation, the Sholler Foundation, Tobacco Settlement Funds from the Commonwealth of Pennsylvania, the Pew Charitable Trust, and the Kresge Foundation.

BBB-109

Telomere length variation in normal epithelial cells adjacent to tumor: a potential biomarker for breast cancer local recurrence – Yun-Ling Zheng

Xin Zhou[1], Alan Meeker[2], Kepher Makambi[1], Ourania Kosti[1], Bhaskar Kallakury[3], Mary Sidawy[3], Christopher Loffredo[1], and Yun-Ling Zheng[1]

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The lack of powerful biomarkers for predicting the risk of breast cancer local recurrence after surgical treatment prompted us to carry out this study in search for better biomarkers. In this study, we discovered that small telomere length variation (TLV) in normal breast epithelial cells adjacent to tumor is significantly associated with an increased risk of breast cancer local recurrence (odds ratio [OR] = 5.1, 95% confidence interval [CI] =1.2- 22.2). The 10-year recurrence free survival rate was also markedly better in patients with large TLV compared with patients with small TLV (80% vs 33%). If confirmed by further studies, TLV in normal epithelial cells adjacent to tumor, in combination with other biomarkers, could be applied to clinical practice to guide the therapeutic decision making in the management of early breast cancer patients.

This study is supported by a grant from Susan G Komen for the Cure (BCTR0707157) and by The Clinical Molecular Epidemiology Shared Resources and The Histopathology and Tissue Shared Resource of Lombardi Comprehensive Cancer Center (NIH grant P30 CA51008).

BBB-110

Novel Molecular MRI Approach for Assessment of Brain Tumors and Radiation Response – Jinyuan Zhou

Jinyuan Zhou[1,4], He Zhu[1,4], Michael Lim[2], Lindsay Blair[3], Alfredo Quinones-Hinojosa[2], Silun Wang[1], John Laterra[3], Peter B. Barker[1,4], Peter C.M. van Zijl[1,4], and Jaishri Blakeley[3]

Departments of [1]Radiology, [2]Neurosurgery, and [3]Neurology, Johns Hopkins University; [4]F.M. Kirby Research Center for Functional Brain Imaging, Kennedy Krieger Institute, Baltimore, MD, United States

APT imaging is a type of recently emerged chemical exchange saturation transfer (CEST) MRI (1), in which amide protons of endogenous mobile proteins in tissue (such as those in the cytoplasm) are detected (2,3). In this abstract, some early results of imaging of malignant gliomas and response to therapy are presented. Fourteen brain tumor patients were recruited. All patients provided written informed consent as required. In all cases (n = 5) with Gd-enhancing high-grade gliomas, Gd-enhancing tumor cores on the post-contrast T1w images were consistently hyperintense on the APT images, compared to contralateral normal-appearing white matter (CNAWM). Interestingly, in two high-grade gliomas without Gd enhancement, which may be mistaken for low-grade, foci of APT hyperintensity were clearly visible within the lesions. Note that absence of Gd enhancement has been reported to occur in ~10% of GBM and ~30% of anaplastic astrocytoma. In addition, for all low-grade gliomas, including one with Gd enhancement, the APT signal was low (iso-intensity to mild hyperintensity) within the lesion. The average APT signal intensities were significantly higher in the high-grade gliomas than in CNAWM ($p = 0.008$) and in the low-grade gliomas ($p = 0.03$). Finally, our ongoing clinical studies showed that the APT approach may distinguish between active glioma (APT hyperintense) versus treatment effects (low APT or isointense) non-invasively, as demonstrated recently in animal models (4). In summary, APT appeared to be more specific than Gd-T1w for active tumors. The APT signal may be a valuable imaging biomarker to identify the spatial extent and pathological grade (high or low) of active high-grade gliomas. (1) Ward et al. J Magn Reson 2000;143:79. (2) Zhou et al. Nature Med 2003;9:1085. (3) Zhou et al. Magn Reson Med 2008;60:842. (4) Zhou et al. Nature Med 2011;17:130.

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Poster Abstracts:

Technologies and
Prototypes Demonstration

TD-A

SWNT-Paper Sensor – Christine Andres

TD-B

Low-Cost Optical Biosensing for Global Health – Joshua Balsam

Joshua Balsam[1,2], Dr. Hugh A. Bruck[2], Dr. Avraham Rasooly[1,3]

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To address the growing needs of global health, sensitive, low cost, simple, and portable medical diagnostic point of care detectors are needed. Many medical diagnostic assays are based on optical detection in devices that are suitable only for laboratory environments. We describe here a multi-wavelength fluorometer based on a simple, low cost imaging platform with sensitivity and capability similar or superior to several current commercial devices. These devices include a commercial plate reader (Tecan Infinite m1000), a micro-array reader (GenePix 4000B), and a fluorescent microscope.

The portable, battery-operated Webcam-based fluorometer system consists of five modules: (1) a CMOS Webcam to monitor light emission, (2) a stage used to perform plate assays, micro-array analysis, or microscopy, (3) filters and multi-wavelength LED or laser illuminator for fluorophore excitation, (4) a portable computer to acquire and analyze images, and (5) image stacking software for image enhancement.

For plate assays, webcam results were compared to results from a CCD astronomical camera and a plate reader using the same plate assay. Our data suggests that when used in a single frame mode, the CMOS webcam fluorometer limit of detection (LOD) is 1000 nM compared to a LOD of 30 nM for the CCD camera and 60 nM for the plate reader. However the use of the webcam in a video mode combined with image stacking enhancement enables the LOD to be reduced to 30nM, which is the same as the far more expensive (~100X) CCD camera. A schematic diagram and photograph of the device in this configuration can be seen in Figure 1.

The same webcam is also converted to a low cost florescent microscope with illumination at 390-650nm and with magnification of approximately 500X which can bring costly florescent microscopy to the global health setting.

The third application of the platform is for microarray analysis. Here a commercial uncooled CCD imager is currently used, and the webcam platform is being adapted. Microarrays are very large arrays of recognition ligands, such as oligonucleotide, cDNA, protein, peptide, antibody, carbohydrate, tissue, or aptamer, immobilized (chemically bonded) at defined locations on a solid matrix. Microarrays are primarily used for DNA analysis. Microarrays have a great potential for molecular diagnostics. The use of a webcam based microarray reader may bring molecular diagnostics to the global health setting.

To make use of the webcam based detectors, we developed an array of Lab on a Chip (LOC) devices which enable a user to perform complex biological assays without a laboratory.

The data presented here suggest that the most basic, simple, and lowest cost webcam can provide sensitivity similar or superior to a sophisticated state-of-the-art plate reader, and thus may enable low cost, portable, point-of-care testing to be realized for various optical and fluorescent-based medical diagnostic assays to address mounting Global Health needs.

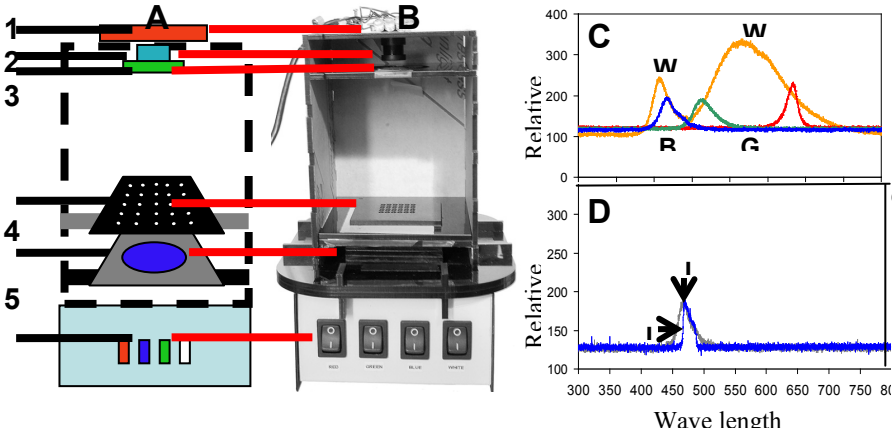

Figure 1: Webcam based plate assay fluorometer A). a schematic configuration of the Webcam based fluorometer with the main system components highlighted in the schematic: [1] a webcam camera mounted in a custom build acrylic box, [2] interchangeable lens with a green band pass emission filter [3] mounted on the end of the lens. Black acrylic sample chip [4]. Blue band pass excitation filter [5] and multi-wavelength LED [6]. B) a photo of a webcam based fluorometer**.** C). The excitation **s**pectra (measured by a spectrometer) of the multi-wavelength LED for the (W) white, (B) blue, green (G) and red (R) LED illumination. D). blue LED illumination spectra with (I) or without (II) blue filter.

Molecular Diagnostics at the Point of Testing – Haim H. Bau

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In recent years, there has been a growing interest in point of care testing (PoCT) to provide health care personnel with timely information that facilitates informed decisions; to monitor spread of diseases and contaminants; and to make sophisticated capabilities available outside centralized laboratories such as in poor resource regions. Most efforts in the development of point of testing devices have focused on immunoassays. Advances in new isothermal amplification strategies enable one to develop molecular (nuclear acid-based) diagnostic tests that are just modestly more complicated than immunoassays, but provide much greater sensitivity and specificity. Here, we describe briefly some of the devices that have been developed and the experiments that were carried out at the Micro & Nano Fluidics Lab at the University of Pennsylvania.

The core component of our devices for molecular diagnostics is the integrated, multifunction, isothermal amplification chamber (**Fig. 1**). The amplification chamber (10-20µl volume) enables nucleic acid isolation, concentration, purification, amplification, and detection [1]. The amplification chamber stores encapsulated (thermally-released) dried reagents needed for DNA amplification [2]. When desired (i.e, in the case of low abundance analytes), the sample volume can far exceed the amplification chamber volume. The pre-stored reagents (not shown in **Fig. 1**) are released and hydrated, just in time, when the chamber's temperature exceeds ~55˚C. Arrays of amplification reactors can be accommodated on a single substrate to facilitate multi-analyte detection, control, and calibration. To amplify target nucleic acid sequences, we employed loop meditated amplification (LAMP) technology [3]. The devices can accommodate, however, other isothermal amplification schemes.

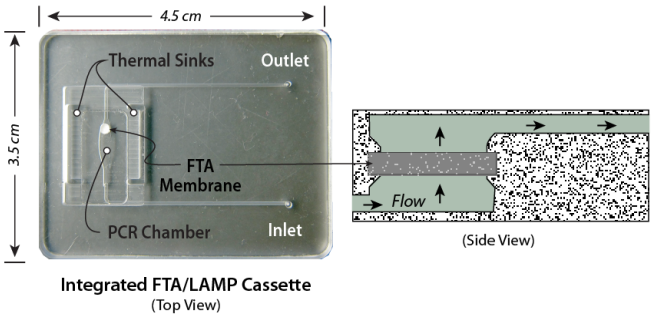

Fig. 1: A module (top view) containing a nucleic acid amplification reactor (left). A cross-section (right) showing sample flows through the isolation membrane.

To demonstrate the capabilities of the amplification reactor depicted in **Fig. 1**, we spiked HIV-1 virus in saliva samples taken from willing (healthy) volunteers [1] and E.-Coli in urine [4]. Our experimental set-up is shown in **Fig. 2**. The devices can operate with a simple processor that allows one to obtain quantitative data (**Fig. 2A and B**) or as completely un-instrumented, qualitative devices (**Fig. 2C and D**). The device shown in Fig. 2C is self-heated [5]. The heating is provided with an exothermic reaction, and the temperature is regulated with a phase change material. The amplicons are detected in real time with an intercalating dye (**Fig. 3A and C**). Alternatively, the amplification products can be discharged onto a lateral flow strip for detection. Our experiments consistently demonstrated a limit of detection better than 100 target molecules / ml sample.

We anticipate using the devices for, among other things, monitoring the viral load of patients undergoing HIV therapy, identifying drug-responsive and drug-resistant bacteria in stool, urine, and other body fluids, and monitoring the safety of food and water supplies. With modifications, the devices might be used to detect the presence of cancer cells in body fluids and to construct gene expression profiles.

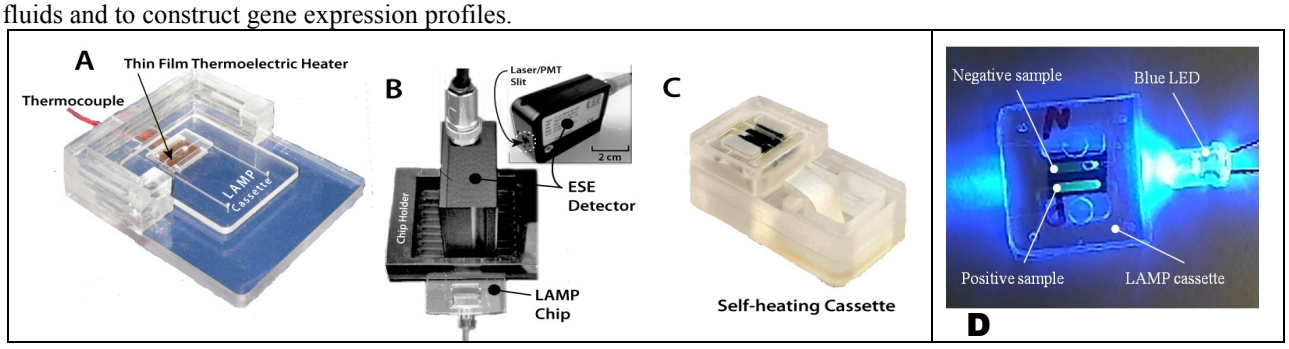

Fig. 2: The set-up used for proof of concept experiments. (A) Photograph of the processor for real-time amplification and detection with electrical heating. The cassette holder is equipped with a thin film resistance heater, a thermocouple,

and a seat for the detector [1,4,5]. (B) The fluorescent signal is excited and detected with a portable, compact (match-box size, Qiagen ESE Fluo Sens SD 003) optical reader. In the future, this reader may be replaced with a blue LED and a smart cell phone camera (see D). (C) Photograph of a cassette heated with a self-regulating exothermic reaction chamber (no electrical power is required) [5]. The amplification reactor is maintained at 60-65oC independent of the ambient temperatures. (D) Feasibility demonstration of monitoring fluorescent emission with a cell phone camera. The devices in (C) and (D) feature two reactors, but can contain an array of amplification reactors for concurrent detection of multiple pathogens and for control, calibration, and quantification.

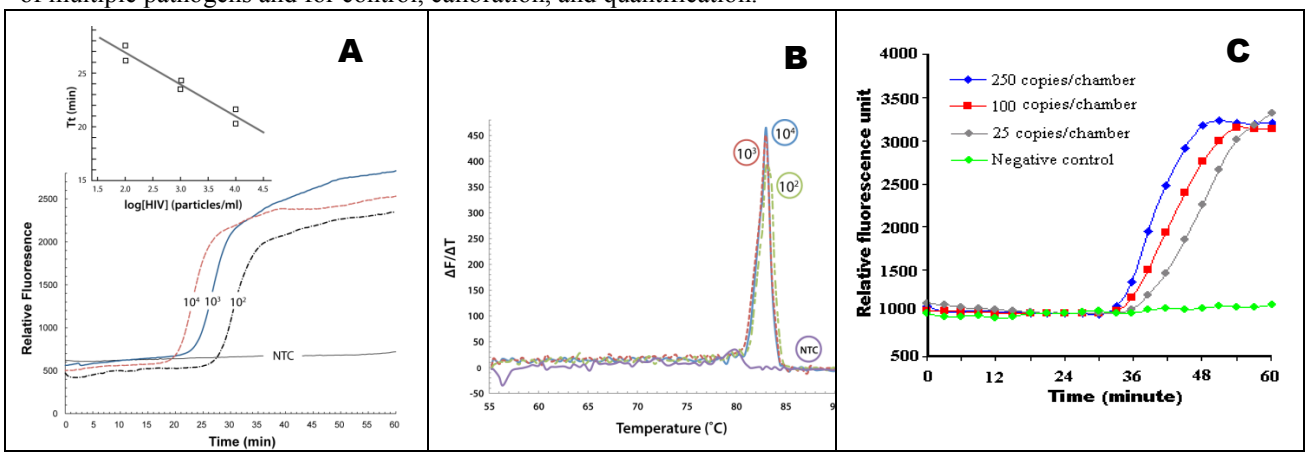

Fig. 3: (A) Real-time monitoring of Reverse Transcription LAMP of saliva samples laden with 10^4, 10^3, 10^2, and 0 (negative control) HIV particles / ml [1]. Inset: The threshold time Tt as a function of the HIV concentration (particles/ml). The threshold time is used to quantify the target concentration. (B) A melting curve: the derivative of the fluorescence intensity with respect to the temperature is depicted as a function of the temperature when the analyte consisted of 10^3, 10^2, 10 and 0 (negative control) HIV particles in the reaction chamber. The peak occurs at a melting temperature consistent with the length of the target amplicon. (C) Real time detection of Escherichia coli DNA in the LAMP cassette [4]. The experiments were carried out with cassettes similar to the ones in Fig. 1 and the set-up shown in Figs. 2 A and B. Similar performance was obtained with the self-heating device [5].

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TD-D

Powering the Medical Devices in the Global Health Setting – Chen, Ellen

Ellen Chen, ABS, Inc.

TD-E

MEMS/Nanotechnology: Tip sensor platform for disease diagnosis and biomarker discovery – Jae-Hyun Chung

Dr. Jae-Hyun Chung: Assistant Professor, Mechanical Engineering at University of Washington (micro/nano fabrication and molecular assembly using an electric field)

Dr. Kyong-Hoon Lee: CTO at NanoFacture, Inc, Bellevue, Washington (biosensors and electrochemistry)

The presented technology combines mechanical and electrohydrodynamic concentration, affinity binding, and capillary action in novel fashion, with unprecedented results. The major innovation is in the concentration of target biomarkers onto a microscale- or nanoscale tip for florescence detection. The presented system concentrates particles to a microtip by using mechanical flow, an electric field, binding affinity, and capillary action. Target analytes in a sample are enriched by electrokinetic flow from location 1 to 2 in Figure 1. The concentrated targets are further attracted to the tip by a dipole moment of polarized targets (dielectrophoresis), transporting targets from location 2 to 3. Specific binding of the targets to the tip is then stabilized by probe molecules. Additional selectivity is conferred by capillary force through the withdrawal of the tip out of the solution. The capillary force excludes molecules and particles that are greater than the diameter of the tip, thereby removing larger particles that associate non-specifically with the tip.

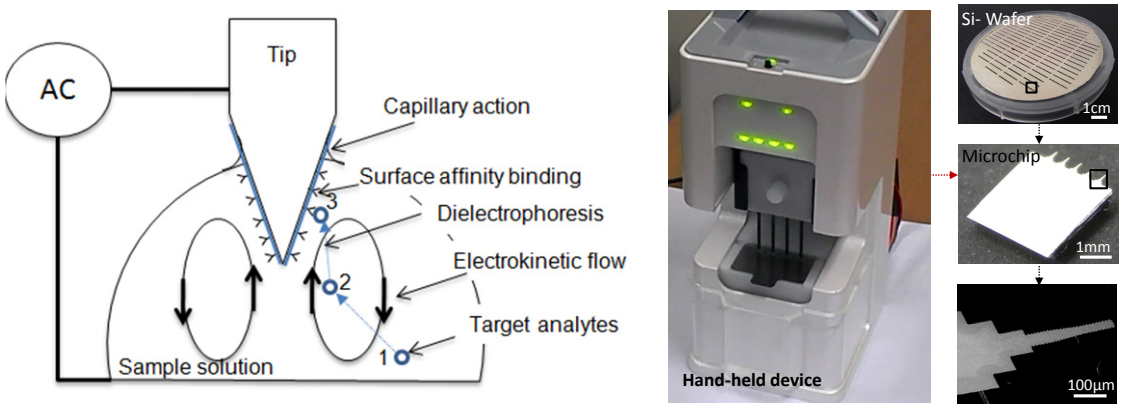

Figure 1. Working principle of a tip sensor platform with a prototype device for DNA concentration and microtips.

Sample preparation: The prototype device shown in Figure 1 is the device that concentrates DAN on a microtip surface. The microtips are immersed with an electric field and withdrawn from the solution. Four samples are processed in one batch. The captured DNA can be stored at room temperature with a dried form. The total time for extracting genomic DNA for buccal swab samples is 20 minutes. The performance for DNA preparation is equivalent to commercially available kits. Through this device, genomic DNA is ready for PCR detection without centrifugation step. A field deployable protocol allows for DNA preparation within 5 minutes from saliva. The hand-held device can be battery operated.

Bacterial detection for global health: The tip sensor has been developed for tuberculosis diagnosis with low cost. Pathogen cells in fluid samples are rapidly concentrated onto microtips, where they are easily detected by a fluorescence microscope. Preliminary data demonstrate the feasibility of this approach when applied to MTB cells in viscous sputum samples. The 25-min process with less than $5 is amenable to POC use and detects MTB with sensitivity equivalent to PCR. The current work focuses on the development of an automated platform that integrates the tip concentrator (Fig. 1) with a fluorescence detection unit.

Vision for low-cost cancer diagnosis: We envision this tip enrichment system as a fundamental tool to provide solutions for early cancer diagnostics and biomarker discovery, in particular, of global health. Due to the simple device action without centrifugation steps, the device will allow the detection of circulating tumor cells, DNA, and other biomarkers with low cost. The major functions of this system are (1) high throughput enrichment and transfer of cells, nucleic acids, proteins, and other biomarkers (2) multiplexing platforms for fluorescence microscopy, electron microscopy, mass spectrometry, etc. and (4) biobanking and preservation of targets.

TD-F

Ultrasound and Portable X-Ray Technology for Global Health – Brian Garra

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The diagnosis of cancer and other medical/surgical conditions has become heavily dependent on radiography and advanced cross-sectional diagnostic imaging over the past three decades. Under-resourced countries in the developing world have largely not shared in these technology advances so that cancer diagnosis remains largely dependent on physical examination often resulting in late or misdiagnosis and poor treatment outcomes. Of the advanced imaging modalities available, only ultrasound can be widely deployed to low resource environments because of low power drain, portability of equipment, and lack of radiation shielding requirements. Many relatively low cost portable ultrasound systems are now available and the price for such systems is dropping with systems costing $1,000-$2,000 on the horizon. Low cost image transmission and storage solutions are also being developed.

X-Ray technology is also decreasing in cost (about $15,000) but remains more difficult to deploy due to power (10-20A), image receptor cost (including processing for film), storage and shielding difficulties. Low cost mobile mammography is an important need for breast cancer diagnosis and is gradually becoming more available. Even portable computed tomography (CT) is becoming increasingly available. CT in particular requires contrast agents and other supplies and equipment to be effective that increase the cost and complexity of deployment. This will limit CT use to larger cities and hospitals for some time to come.

When introducing new imaging technology for cancer diagnosis, it is important for the interested organizations to collaborate to make certain that appropriate ancillary diagnostic tests are available and that cancer treatment is also available. In many cases lack of treatment resources will dictate a less aggressive approach to treatment, often aiming for palliation instead of cure, so that a larger number of patients will have access to some sort of treatment.

Hand-Held Optical Imaging Technology – Anuradha Godayarty

Dr. Anuradha Godavarty & Dr. Sarah J. Erickson

Device Description: Hand-held based optical imaging devices are recently developed which are portable and patient-comfortable. However, the NIR devices developed to date have not performed 3D tomography since they are unable to coregister the image to the tissue geometry. In our Optical Imaging Laboratory, we have developed a handheld optical imager which has automated coregistration facilities to enable 3D tomographic imaging. The device employs a flexible probe head that can contour to any tissue volume/curvature and image large tissue areas in near real-time to allow a functional (i) B-scan of the tissue (like an ultrasound), as well as (ii) 3D tomographic scan (like an MRI), upon employing the developed novel imaging approaches.

Principle of operation: The optical imaging technology utilizes non-ionizing near-infrared light to see few cm deep within the tissue and differentiate different tissue types (e.g. normal vs. diseased). The light is similar to that from a laser pointer.

The hand-held device (see Figure 1) works in conjunction with its proprietary coregistration software. It has been developed to image large tissue volumes using a flexible probe face that contours to different surface tissue curvatures. Because the device has a flexible head that contours, certain body parts can be better visualized in three dimensions. The three-dimensional (3D) tomographic ability of the device has been demonstrated on large tissue phantoms using a fluorescence-enhanced imaging technique. Simultaneous illumination and detection from multiple point locations is carried out to reduce the overall imaging time. The instrumentation can acquire both continuous wave (CW)–based and frequency domain–based optical measurements as required. Frequency-domain optical measurements provide more information about the tissue and also better depth information of the targets (or tumors) over the CW based measurements. CW based has a faster imaging time, making it a good clinical approach for near real-time imaging studies.

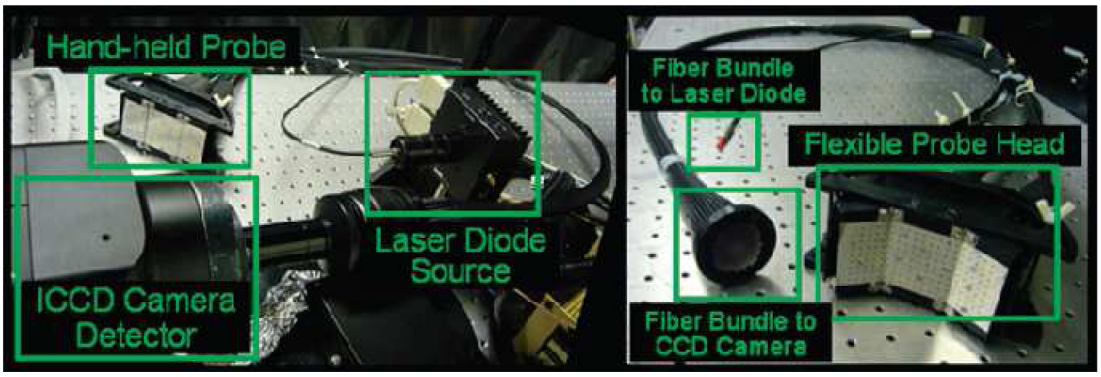

Figure 1. Handheld probe–based optical imaging system showing the handheld probe is fiber-optically coupled to the laser source and ICCD camera (left). The probe face is flexible to contour to different tissue curvatures (right).

In summary, the non-invasive hand-held optical device with the following features:

1. Flexibility to image any given tissue curvature and volume over larger surface areas
2. Portable device (see schematic in Figure 2) that can be available in a physician's office apart from radiology centers
3. Ability to perform near real-time imaging of large tissue areas for immediate results
4. Ability to perform both 2D surface as well as 3D mapping of tissue geometries in a matter of few seconds.
5. Capability to improve patient comfort from avoiding tissue compression (as in x-rays)
6. Ability to perform 3D volumetric analysis of imaged tissue geometries (e.g. tumor localization studies etc.)

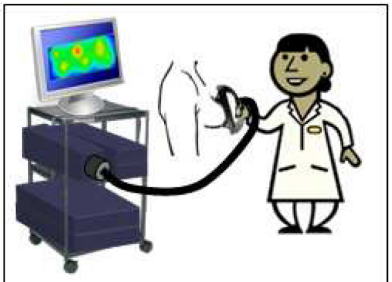

Figure 2 – Schematic of portable hand-held optical device.

The unique features of our device that do not exist in other handheld optical devices (in the absence of a second imaging modality) are highlighted in gray (see above).

Potential Utility of the Technology: The technology has multiple applications. The primary application of interest is breast cancer imaging at various stages of the disease (e.g. diagnosis, prognosis/tumor treatment response studies). The secondary indication for this technology will most likely be sports injuries or disease progression monitoring. Ankle injuries and concussions are few of the most common sports injuries where our device is expected to have important applications.

Other potential applications include:

- Sentinel Lymph Node mapping
- Function Brain Mapping in neurologically challenged populations (e.g. epilepsy, autism, cerebral palsy)
- Lie Detection Tool
- Drug delivery
- Any body tissue imaging (along curvatures)

Potential Applications for Global Health: Our technology has wide commercial applications (as listed above) across a multitude of industries on a global scale but as a starting point, our initial focus in breast cancer. Breast cancer affects approximately 1 in 8 women and is one of the leading causes of cancer related deaths for women in the industrialized world. Worldwide the diagnostic imaging market is $15.8 billion[1] and is expected to grow by six percent a year.[2] Specifically the U.S. market for mammography equipment sales was estimated at $339 million in 2002 with an expected compound annual growth rate of more than eight percent. Globally, mammography equipment sales are expected to grow at more than 20 percent per year[3], and reach $1.1 billion by 2015.

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Gene-Z: A Rapid & Inexpensive Gene Analyzer for High-End Diagnostic Applications – Syed Hashsham

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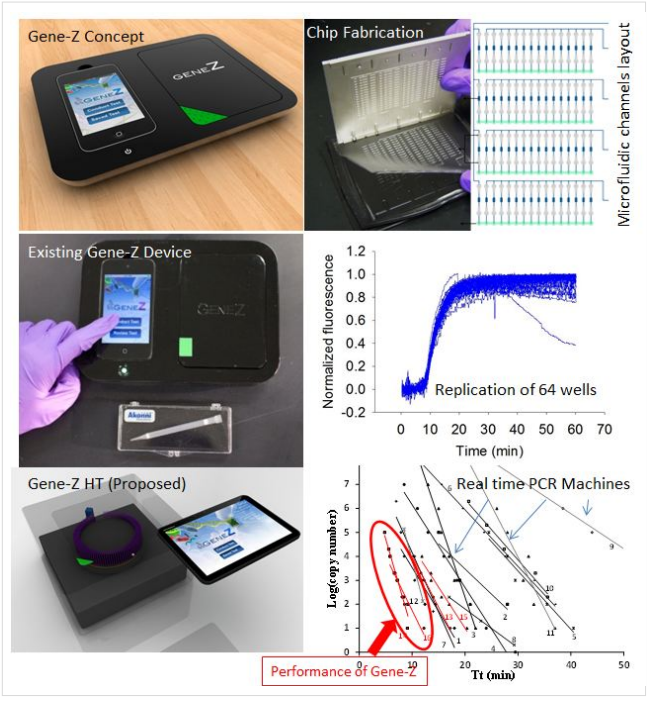
SUMMARY

Quantification of copy number of viruses during treatment, genotyping and multiplexed screening, mutation detection, cancer marker measurements, and microRNA profiling are all specialized assays currently possible only by a handful of devices ranging from ~$50,000 (e.g., LightCycler, Third Wave Technology, Cobas Amplicor) to ~$100,000 (e.g., TaqMan PCR, GeneXpert) with assay cost ranging from $50 to $250. With the ever increasing number of cancer patients, the number of HIV cases crossing 40 million globally and drug resistant TB expected to infect more than 2 million people by 2015, the need to bring down the cost and take these capabilities to the masses is urgent. Substantial progress has been made in certain areas e.g., Xpert MTB/RIF assay can measure the mutation causing rifampicin resistance in 2 hours compared to months taken by the susceptibility assay. Such devices are the method of choice at centralized screening facilities with abundant resources and will most likely remain so. Our aim is to complement such progress by much lower cost but equally powerful devices and approaches so that more people can be served with the available resources.

We have developed a device that is ~1/50th to 1/100th of the cost of currently available devices (and assays) but without compromising the power of the assays. In terms of functionalities, it is akin to a hand-held real time PCR machine but uses real time loop mediated isothermal amplification (RT-LAMP) assays in credit card size microfluidic chips. In its current version (see Figure below), it is capable of carrying out 64 assays. In the high throughput version (Gene-Z HT), it will be able to carry out many assays for hundreds of specimens within an hour. These application-specific chips are extremely inexpensive (less than 10 cents) and simple to fabricate. We have validated these devices for key applications. Specifications of Gene-Z are: i) **real time quantitative measurements** based on Syto-82 fluorescence, ii) sensitivity: 1-10 copies per well, iii) assay time: 10 to 30 minutes, iv) assay cost: $1-$10 per chip available in freeze dried format for field use (chips will be disposable), and v) device cost: $1,000. Its control, data collection, and analysis software is developed on iPod Touch and a high throughput version (Gene-Z HT) using Google's Android OS is under development. The overall device is similar in size and weight to a Tablet PC or iPad. Its adaptability to add new assays is unsurpassed. We believe that with its proper and timely implementation, the impact of such a device on human health could be tremendous. Some of the key microfluidic chips that we are developing (varying stages) on this platform are summarized below.



1. ***Hand-held MDR TB Analyzer:*** According to the NIAID, "Diagnostic tools that are suitable for use in field sites with limited technical and personnel infrastructure" are a necessary component to fighting the spread of multidrug-resistant and extensively drug resistant (MDR/XDR) TB. "Developing and testing reliable technologies to rapidly diagnose all forms of TB and to identify drug resistance" is one of the six critical areas identified by NIAID as part of the coordinated global effort to combat TB. In TB -endemic countries, up 23.4% of the cases are XDR TB. In 2006, 9.2 million new TB cases were reported worldwide, of which, 1.7 million resulted in death. Of these cases, approximately 0.5 million were drug-resistant TB, and most people who contract this type of TB die. The reason for the high mortality rate among patients with drug resistant TB is the current unavailability of point-of-care diagnostic tools to distinguish the strain of TB. This differentiation is critical to providing proper treatment. With some

additional development (one year, $700,000), Gene-Z is capable of providing MDR/XDR TB diagnostic capabilities at a fraction of the cost currently incurred.

2. ***Viral Load Determination during HIV Treatment:*** Quantification of viral load during treatment of HIV is critical to assess the efficacy of treatment. A viral load chip developed with freeze-dried or trehalose preserved field deployable chip may help determine the viral load targeting a number of genes at a sensitivity of at least 50-100 copies per ml. Primers could be designed for both HIV viral load and genotyping resistance using NCBI viral genotyping tool, HIVdB at Stanford, and our own FunGene primer design tool.

3. ***Dengue/Chikangunya Monitoring:*** Importance of field diagnostics for these agents is important for multiple reasons. Blood sugar monitors are too commonly available with sample strips that use ~ 1 μL of blood and a few seconds to yield results. With dengue virus abundance in 1000 viruses per μL of blood specimen and easily available isothermal amplification techniques, it is not clear why similar devices are not available to diagnose Dengue and Chikangunya viruses in blood in a fraction of the time and cost that is incurred today. Using Gene-Z, we could develop and validate a low cost (<Rs. 50 or $1) chip to diagnose Dengue using approximately half a dozen genetic markers and reverse transcriptase LAMP for DEN-1, DEN-2, DEN-3, and DEN-4 genes. Because the device is already available, most of the development needed is towards field validation of the chip.

4. ***Real time monitoring of cancer markers and profiling of microRNAs:*** Cancer-specific markers (DNA or RNA) can be measured as easily as some of the above targets. However, microRNAs profiling is a completely different application compared to the type of applications described above. We have included it here as an example of the versatility of Gene-Z^{TM}. MicroRNAs are small molecules (20-30 nucleotides), heavily studied as markers of certain types of cancer. In the mirDB database, there are approximately 1,000 known human microRNAs today. Measurement of microRNAs has been difficult due to its small size. Initially, hybridization-based screening was the only option but now real-time PCR based measurement techniques are also available which are based on extension of the molecule followed by amplification. As a proof-of-concept, we have modified the LAMP assay to measure microRNAs. This combined with the higher density chip and CCD imaging system will allow us to monitor all microRNAs in a rapid and low cost manner, within ~2 hours.

5. ***Rapid Antibiotic Susceptibility Assay Combined with Antibiotic Resistance Gene Screening:*** Using this device we are also developing a rapid (5-10 generation time which is 2-3 hr for some of the fast growers) Antibiotics Susceptibility Assay in a microfluidic chip. Combined with some rapid bacterial enrichment approaches, we believe that the approach of assessing AST by growth as well screening the cells for genetic markers is unique and will be able to provide a critically needed technology to guard against the spread of antibiotic resistance bacteria (e.g., NDM-1).

Circulating Tumor Cells in Microfluidic Devices for Global Health – Samir Iqbal

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Early detection and isolation of circulating tumor cells (CTCs) can enable early cancer diagnosis for better intervention and effective therapeutics. Aptamers are alternative affinity reagents that have comparative affinities as antibodies but better specificities. Antibodies also depict high levels of off-target cross-reactivity and stability issues. Aptamers can be custom synthesized and modified easily.

Epidermal growth factor receptor (EGFR) is the most frequently overexpressed receptor in all human malignancies. The expression level of EGFR in cancer cells can be over 100 times higher than that in normal cells. It is also an attractive target for cancer therapy.

We define aptamer-based detection and isolation strategies directed against EGFR overexpressing human Glioblastoma (hGBM) cells [1-3]. To test the sensitivity and specificity, anti-EGFR aptamers were first immobilized on chemically modified glass substrates (Fig. 1). A simple PDMS block with microfluidic channel was made and bonded to the glass substrate (Fig. 2). The cells were injected through the microfluidic channel and it was found that surface functionalized with anti-EGFR aptamers could capture hGBM cells and enrich hGBM cells from a mixture of fibroblasts (Fig. 3). Moreover, the change in cell shape and cellular activity on aptamer surface can serve as a novel way of identifying cancer cells (Fig. 4). We also mimiced the nano-scale topography of basement membrane which anchors a cancer cell to its loose underneath connective tissue (Fig. 5). The nanotextured surfaces have more effective area and less steric effect resulting into immobilization of many more aptamers, favorable for cell isolation. The topography also resulted in differential cell spreading showing much more distinct behavior (Fig. 6).

The nanotextured surfaces can significantly improve cancer cell isolation efficiency without significant decrease in specificity. In a global health perspective these are inexpensive approaches that can have much wider effects towards cost-effective and ubiquitous detection strategies. Such approaches provide a much better probability of capturing and isolating small number of tumor cells from solution. In brief, the anti-EGFR aptamer functionalized substrates can be deployed globally for identification and isolation of CTCs from peripheral blood, dramatically changing intervention and prognosis of metastasis.

Fig. 1. Schematic of PDMS channel which was bonded on glass slides.

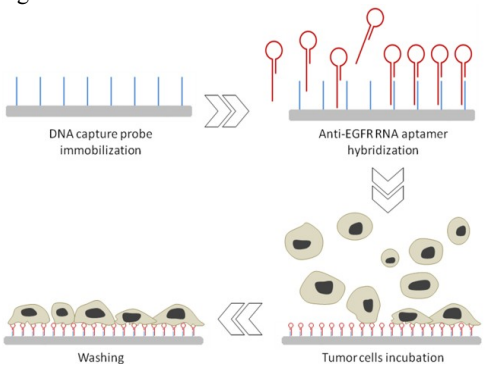

Fig. 2. Steps of experiment [1].

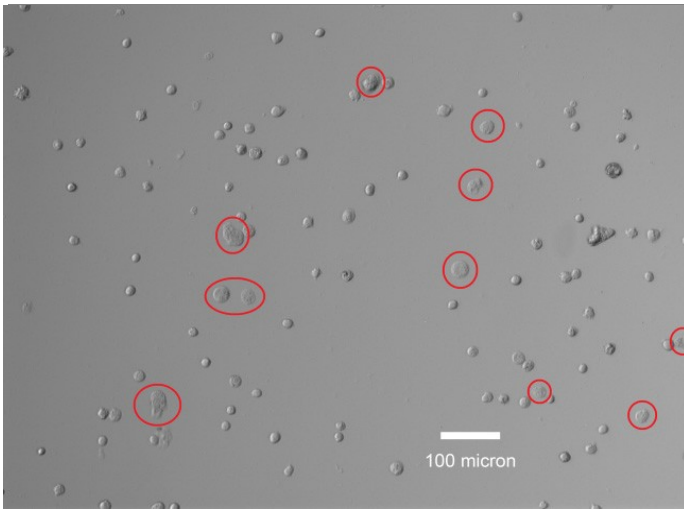

Fig. 3. Selectively captured and enriched hGBM cells on the anti-EGFR aptamer functionalized glass substrates. The circles indicate a few fibroblasts that were captured [1].

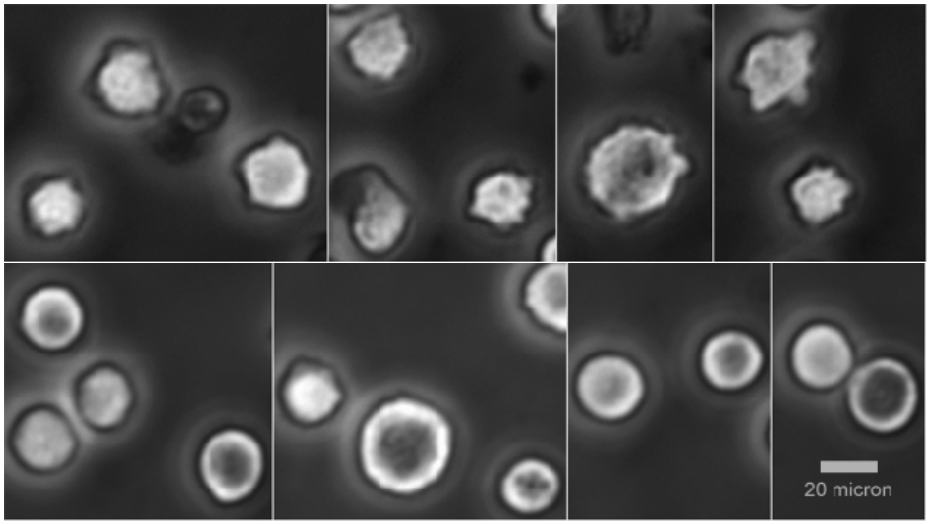

Fig. 4. The changes in shapes of mouse-derived tumor cells captured on anti-EGFR aptamer functionalized substrates (top 4 micrographs) and mutant aptamer functionalized surface (lower 4 micrographs) after 30 min cell seeding [1].

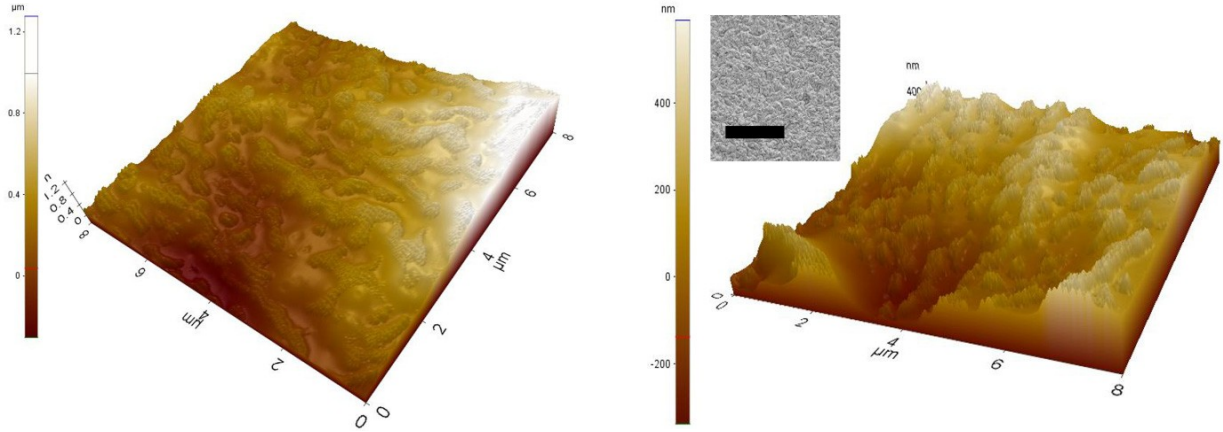

Fig. 5. AFM micrographs of a nanotextured PDMS surface (left) and a nanotextured PDMS surface (right) after chemical modification. Inset shows Scanning Electron Microscope (SEM) micrograph of nanotextured PDMS (Scale bar: 100 µm) [2].

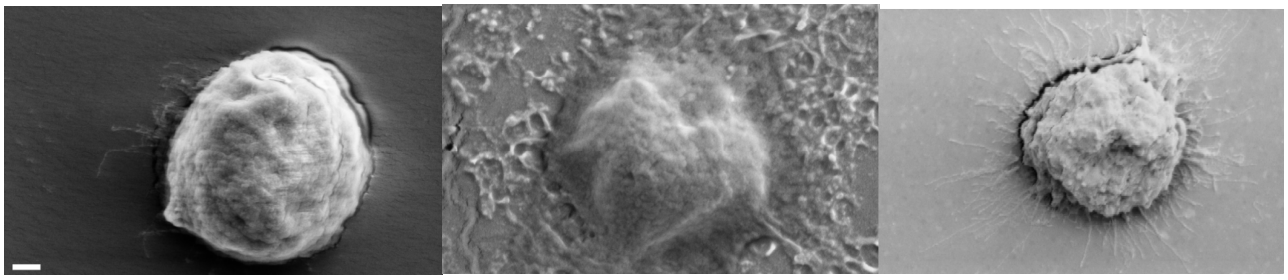

Fig. 6. SEM micrograph of captured cancer cells on PDMS, nanotextured PDMS and glass substrates respectively (from left to right) [2]. Scale bar of 1 µm is same for all micrographs.

References:

1. Y. Wan*, et al.*, *Surface Immobilized Aptamers for Cancer Cell Isolation and Microscopic Cytology.* Cancer Research, 2010. **70**(22): p. 11.
2. Y. Wan*, et al.*, *Nanotextured substrates with immobilized aptamers for cancer cell isolation and cytology.*CANCER, 2011: p. 10.1002/cncr.26349.
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TD-J

Handheld optical imaging scanner for advanced point of care diagnostics – Woonggyu Jung

Woonggyu Jung[1], Jeehyun Kim[2], Daniel T. McCormick[3], Cac T. Nguyen[1,4], Zita Hubler[1,5], Eric J. Chaney[1], Samir I. Sayegh[6], Michael Novak[7], Charles N. Stewart[8], Stephen A. Boppart[1,4,5,7,9]

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We have developed the new concept of point-of-care handheld diagnostic instrument using optical coherence tomography (OCT) for use in a fast-paced clinical environment. The most unique feature of our handheld scanner is that a single probe can image various tissues such as the cornea, retina, tympanic membrane, and the skin. This instrument enables the visualization of both surface and cross-sectional structure of tissues. Our handheld imaging probe also provides user friendly functions such as sound feedback, button control, and confirmation of the imaging location via a small display to manipulate probe and focus positioning during screening and diagnostic procedures. In this technical demonstration, we will show the latest version of handheld optical imaging scanner and experimental results to evaluate the clinical value of our device.

TD-K

Shrink-Film Microfluidics for Inexpensive and Rapid Devices – Micelle Khine

The challenge of micro- and nano-fabrication lies in the difficulties and costs associated with patterning at such high resolution. Instead of relying on traditional fabrication techniques largely inherited from the semiconductor industry we have developed a radically different approach. We pattern at the large scale, which is easy and inexpensive, and rely on the heat-induced relaxation of pre-stressed polymer sheets – commodity shrink-wrap film – to achieve our desired structures. Using this approach, we have demonstrated that we can create fully functional and complete microfluidic devices with integrated nanostructures for molecular capture and sensing, printed electronics, and even optical components, all within minutes. These devices which can be use for biomedical assays cost only pennies to make and obviate the need for dedicated costly equipment. Because this process is compatible with roll-to-roll plastic processing, it is also scalable and cost-effective enough for point of care applications.

TD-L

Detection of Kaposi's Sarcoma causing Herpes Virus using Lab-on-a-Syringe Technology – Matthew Mancuso

Matthew Mancuso[1], Li jiang[2], Ethel Cesarman[3], David Erickson[2]

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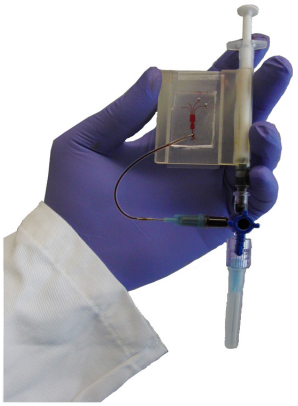
Kaposi's sarcoma (KS) is the most common cancer in several African countries and is a dangerous threat to individuals with AIDS who have a greatly increased risk of developing the disease. The cause of KS is Kaposi's sarcoma herpesvirus (KSHV, also called HHV-8), and for accurate diagnosis of KS, KSHV must be identified. While accurate diagnosis is enabled in first-world hospitals through advanced laboratory medicine such as immunohistochemistry or PCR, developing-world doctors struggle to diagnose KS with high accuracy due to reliance on sub-state-of-the-art techniques. Here we propose to develop easily operated and robust technology for the detection of KSHV in resource limited settings. Our approach involves the creation of Lab-on-a-Syringe technology with sample in, detection out capability. The goal is to create easily operated assays which can detect KSHV virus in biopsy samples and provide an accurate diagnosis using minimal external infrastructure.



TD-M

Low Cost Medical Devices Combined with Telemedicine Reduce Health Disparities between Developed and Developing Countries – Nenad Markovic

Dr. Olivera Markovic[1], Dr. Nenad Markovic[2], Dr. Oleg Panashchenco[2], Sarjit Bains[3], Ms. Jane Jing[4]

[1]Global Academy for Women's Health, Rockville, MD; [2]Biomedical Science Consulting, Rockville, MD; [3]MarkPap India LLC, Rockville, MD; [4]MarkPap Pacific LLC, Rockville, MD

Individual health is one of basic human rights and improving the conditions to maintain and improve this health is one of the basic duties of all responsible governments. In 21st Century, the era of information technology, when health news is instantly distributed all around the world by multiple media, it became generally known that developing countries are paying for their lack of resources with more lives lost, and with worse living conditions in comparison with the developed countries. Globalization of information distribution is only making this disparity more visible and delaying of clear policy on how to reduce it could cost developed countries much more than sophisticated programs to reduce such a disparity between humans based on the difference of the resources in their living areas. Global Health Initiative and M-Health Initiatives are offering such programs. Based on the concept of using modern communication technology between remote point-of- care (sites at any place in the world where health professionals are delivering their services to members of the local communities) and the highly specialized medical centers in developed countries, the promoters of this program are expecting to provide worldwide health care systems that will be more accurate, faster and less expensive than the current medical practice delivered on site of medical needs. Our poster, if this Abstract is accepted, will present the MarkPap System for low cost global cervical cancer screening (cancer detection and diagnostics in service of global cancer control) based on m-health and telemedicine devices integrated into web-based networking available for all areas where the Internet and cellphone connections are active.

To our partners in China and India

TD-N

Photonics based Telemedicine Technologies toward Smart Global Health Systems – Aydogan Ozcan

Aydogan Ozcan, Ph.D.

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Today there are more than 4 billion cell-phone users in the world, and the majority of these cellphones are being used in the developing parts of the world. This massive volume of wireless phone communication brings an enormous cost-reduction to cellphones despite their sophisticated hardware and software capabilities. Quite importantly, most of these existing cellphones are also already equipped with advanced digital imaging and sensing platforms that can be utilized for various health monitoring applications. This impressive advancement is one of the central building blocks of the emerging fields of "Telemedicine" and "Wireless Health". The success of these fields will surely increase the quality of health care and reduce the insurance costs in developed countries like the United States, however, their most important and immediate impact will be to provide breakthrough technological solutions to various Global Health Problems including infectious diseases such as HIV, TB or malaria. Specifically, utilizing this advanced state of the art of the cell phone technology towards point-of-care diagnostics and/or microscopic imaging applications can offer numerous opportunities to improve health care especially in the developing world where medical facilities and infrastructure are extremely limited or even do not exist.

Centered on this vision, in this talk I will introduce fundamentally new imaging and detection architectures that can compensate in the digital domain for the lack of complexity of optical components by use of novel theories and numerical algorithms to address the immediate needs and requirements of Telemedicine for Global Health Problems. Specifically, I will present an on-chip cytometry and microscopy platform that utilizes cost-effective and compact components to enable digital recognition and 3D microscopic imaging of cells with sub-cellular resolution over a large field of view without the need for any lenses, bulky optical components or coherent sources such as lasers. This incoherent holographic imaging and diagnostic modality has orders of magnitude improved light collection efficiency and is robust to misalignments which eliminates potential imaging artifacts or the need for realignment, making it highly suitable for field use. Applications of this lensfree on-chip microscopy platform to high-throughput imaging and automated counting of whole blood cells, monitoring of HIV+ patients (through CD4 and CD8 T cell counting) and detection of waterborne parasites towards rapid screening of water quality will also be demonstrated. Further, I will discuss lensfree implementations of various other computational imaging modalities on the same platform such as pixel super-resolution imaging, lensfree on-chip tomography, holographic opto-fluidic microscopy/tomography. Finally, I will demonstrate lensfree on-chip imaging of fluorescently labeled cells over an ultra wide field of view of >8 cm^2, which could be especially important for rare cell analysis (e.g., detection of circulating tumor cells), as well as for high-throughput screening of DNA/protein micro-arrays.

Technologies to Expand Cervical Cancer Screening Coverage in Low-Resource Settings – Roger Peck

Peck RB[1], Weigl BH[1], Jeronimo J[1]

[1]PATH, Seattle, USA

Human Papillomavirus (HPV) is nearly the exclusive cause of cervical cancer. Each year, over 500,000 new cases are identified and more than 270,000 deaths are attributed to cervical cancer. Developing countries are impacted disproportionately, shouldering 80% of the burden. Cervical cancer is preventable when women with precancerous lesions are identified through screening programs and receive treatment. Cytology-based screening programs have been successful in portions of the world with good health care infrastructure and where women have routine access to the programs. In 2003, PATH initiated the Screening Technologies to Advance Rapid Testing (START) project to address the need for cervical cancer screening tools suitable for use in settings where laboratory infrastructure is poor and access to screening programs are nonexistent or are limited to once or twice in a woman's life. Through the START project, PATH began collaborations with two private-sector companies with ongoing programs in the field of cervical cancer diagnostics to develop novel tests to identify women at risk of developing cervical cancer that would be suitable for use in low-resource settings. The PATH/Qiagen partnership focused on developing an HPV DNA test based on the hc2 technology. The resulting *care*HPV™ test (Figure 1) is a screening test for 14 high-risk HPV types that yields results in approximately 2½ hours in a basic laboratory with minimal infrastructure requirements. Initial studies indicate that the test is easy to perform and has good performance (84.3% sensitivity and 87.5% specificity.) The PATH/Arbor Vita Corporation partnership focused on developing a test for detection of HPV E6 oncoprotein. The resulting AVantage™ HPV E6 Test (Figure 2) uses a lateral flow ("strip") format and detects E6 oncoprotein from three high-risk HPV types (16, 18, and 45). The test yields results in approximately 2 hours and can be performed in a basic laboratory with minimal infrastructure requirements. Initial studies indicate that the test can detect clinically relevant levels of E6 protein expression that predict those women at risk of progressing to cervical cancer. The *care*HPV™ test system and the AVantage™ HPV E6 Test will be presented, and the features and benefits of each will be discussed.

Figure 1: *care*HPV™ test schematic

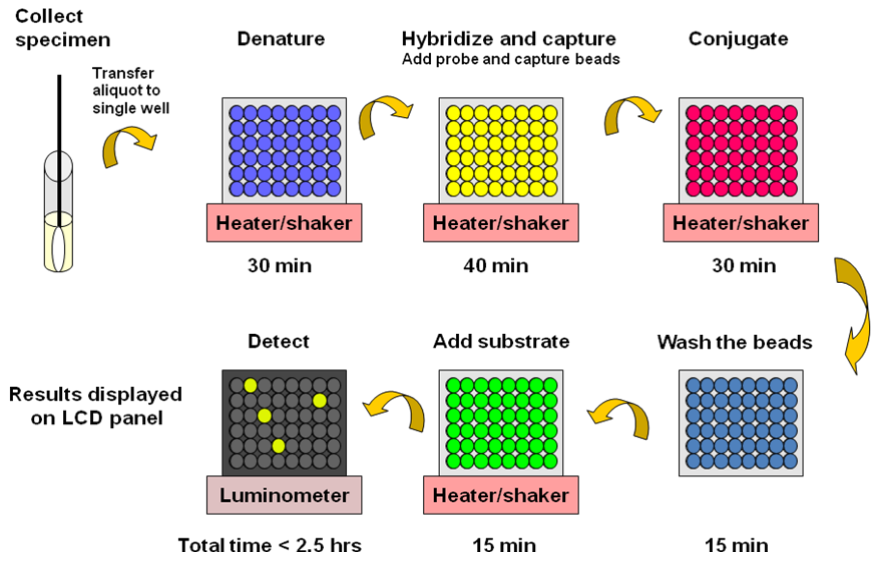
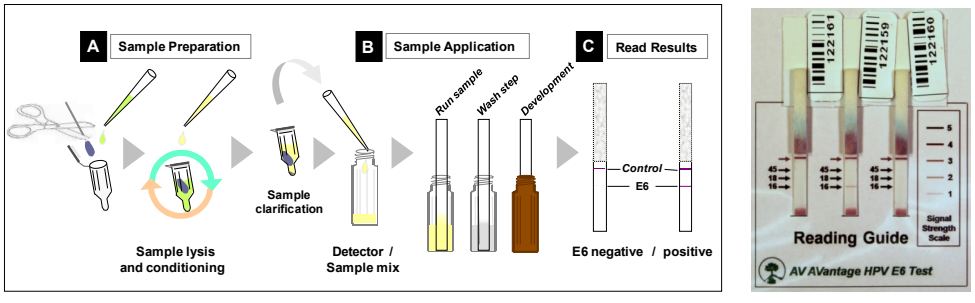


Figure 2: AVantage™ HPV E6 Test schematic



Paper-Based microfluidic devices that contain “fluidic” batteries and “fluidic” timers for conducting quantitative colorimetric assays – Scott Phillips

Scott T. Phillips

Microfluidic devices fabricated out of paper (and paper and tape) have emerged as a promising platform for conducting multiple diagnostic assays simultaneously in resource-limited settings such as the developing world. Certain types of assays in these devices, however, require a source of power to function (examples include: electrochemical assays, quantitative time-based colorimetric assays, etc.). Lithium ion, nickel-cadmium, and other types of batteries have been used to power these devices, but these types of batteries may be too expensive and represent too much of a disposal hazard for diagnostic applications in the developing world. To circumvent this problem, we have designed a “fluidic” battery that is composed of multiple galvanic cells incorporated directly into a multilayer paper-based microfluidic device. The cells can be connected in series and/or in parallel (or both), and when a sample is added to the device, the battery is capable of powering an audible buzzer or a light emitting diode (LED) for use in “fluidic” timers, which are timers that are incorporated directly into the paper-based microfluidic devices as well (*Anal. Chem.* 2010, *82*, 8071). Fluidic batteries were built using silver and aluminum metals with silver nitrate and aluminum chloride salts. The batteries were optimized to give the maximum current and voltage over a very short period of time (<1 min). Four cells were connected, two in series and two in parallel, to give the maximum current and potential of 600 μA and 2.4 V, respectively. This four cell battery, when used in conjunction with a fluidic timer, was demonstrated in the context of a quantitative glucose assay. The four cell battery has a shelf-life of more than five weeks, and has an operating life-time of 8 min, making it a useful source of power for running multiple types of assays on paper.

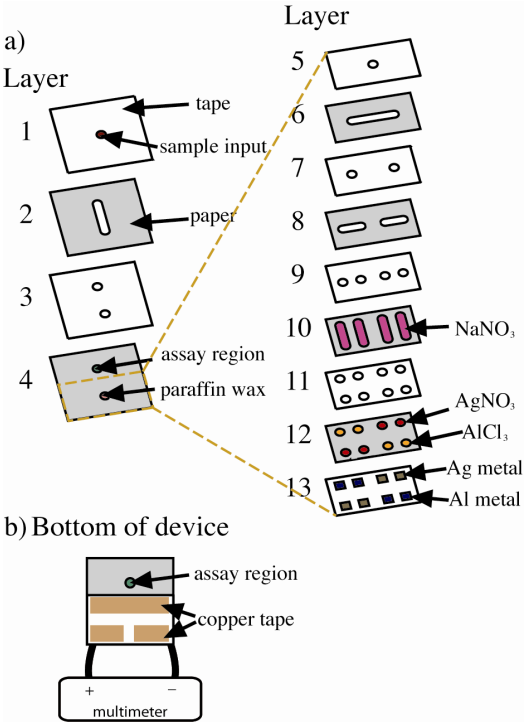


Figure 1. Example design of a four-cell battery in layered paper and tape. The battery in this figure is connected to one fluidic timer (i.e., the paraffin wax) and one region for assays, although many other assay regions can be incorporated as well. a) The layout of the tape and paper for the four-cell battery with a region for an assay. The sample is applied to the sample input region. The assay region contains the assay reagents, and is located at the bottom of the device. The paraffin wax slows the flow of the sample, acting as a timing region. b) Bottom view of a finished device connected to a multimeter. When the device is attached to an LED or buzzer, the electrodes on the LED or buzzer are attached to the same spots as the multimeter, the only difference being that double-sided Cu tape is used to hold the LED/buzzer in place.

TD-Q

Book Presentation – Maja Pleic

Maja Pleic, Harvard University

TD-R

Integrated Microfluidic devices for Assays of Cancer Cell Migration, Invasion, and Protein Expression – Lidong Qin

See abstract TTT-42

TD-S

Demonstration of High Resolution Microendoscope for Cancer Screening in Low-Resource Settings – Rebecca Richards-Kortum

Rebecca Richards-Kortum, Ph.D.

Department of Bioengineering, Rice University, 6100 Main Street, Houston, TX 77005, USA

Today, more than 70% of the world's cancer deaths occur in these low- to middle-income countries, where 80% of patients present with advanced disease at the time of diagnosis. These figures are unlikely to be affected by a widespread infusion of high-level imaging technology in the foreseeable future. Even in developed countries, the presence of diagnostic imaging technology alone does not equate to widespread access. Patients in the US who are uninsured or who have Medicaid insurance are significantly more likely to be diagnosed with late stage cancer, and have significantly lower survival rates than patients with private insurance. At a time when the global incidence of cancer is rapidly increasing and 47 million Americans lack health insurance, there is an urgent need for effective and affordable tools and technologies to facilitate early detection, prevention, and treatment of cancer in low resource settings.

Optical imaging is a new technology which may provide a potential solution to the global need for affordable imaging tools to aid in the early detection and management of cancer. While healthcare providers have traditionally used optical tools such as endoscopes, colposcopes, and surgical microscopes in cancer management, a new generation of instruments is being developed which can detect not just reflected white light, but additional signals arising from cancer biomarkers, carried in the fluorescence, polarization, and narrowband reflectance of light. These systems are capable of examining tissue over a wide range of spatial scales, with widefield macroscopic imaging typically spanning several square-centimeters, and high-resolution *in vivo* microscopy techniques enabling cellular and subcellular features to be visualized. Optical instrumentation is relatively inexpensive, using mass-fabricated components developed by the telecommunications and consumer electronics industries. A second key factor is the recent emergence of multimodal optical imaging systems, simultaneously providing wide-field *and* high-resolution optical imaging, within cost-effective, portable, and even battery-powered formats.

We recently developed a battery-powered, portable system, capable of both widefield and high-resolution digital imaging, and have begun clinical studies to compare its performance against large-scale counterparts. The widefield imaging component consists of a commercially available surgical headlight system modified to include LED illumination for both white light and fluorescence excitation, and a high-sensitivity CCD camera for digital image acquisition. This portable screening system weighs only 3 lb and can alternatively be mounted on a camera tripod. The high-resolution imaging capability is provided by epi-illumination of a flexible 1 mm diameter fiber-optic bundle, with the distal end of the fiber placed in contact with the tissue site to be imaged, following topical application of a fluorescent contrast agent. Fluorescent light emitted from the tissue returns through the same fiber and is imaged onto a high-sensitivity CCD camera. This system was engineered into a lightweight and portable package. Both the widefield imager and the high-resolution microendoscope systems connect to a single laptop computer via IEEE-1394 (Firewire) ports, enabling simultaneous imaging within a LabView-based user interface (Fig. 1). The total cost of components for the combined imaging platform was under $10,000.

Figure 1 presents widefield and high-resolution images of normal human oral mucosa acquired with the multimodal imaging system. In the widefield image (left frame), the autofluorescence of normal tissue is apparent, as well as the microvascular network. The high-resolution fiber-optic probe can be seen in contact with the mucosal surface, approaching from the base of the widefield frame. The high-resolution image, acquired simultaneously, is displayed in

the lower right frame, with the 800 μm diameter field-of-view corresponding to the tissue located beneath the tip of the fiber-optic probe. Following topical application of 0.05% proflavine solution to the probe tip, nuclei appear as discrete bright regions within each epithelial cell. The diagnostic performance of this integrated imaging system is currently being evaluated in pre-clinical studies, in comparison with research-grade optical imaging systems, and against the gold-standard of histopathology.

Cancer is projected to become the world's leading cause of death by 2010, with the burden of disease shifting further towards medically underserved populations in industrialized countries and the developing world. New approaches are required across the spectrum of cancer management, in prevention, diagnosis, treatment, education and care. If developed and tested appropriately, optical imaging technologies can play an important role in several aspects, from providing objective diagnostic screening at the community healthcare level, to enabling pathology guidance in the clinical setting. Importantly, by delivering these technical capabilities within cost-effective platforms, the impact on public health can be magnified through expanding patient access to previously unreachable healthcare systems.

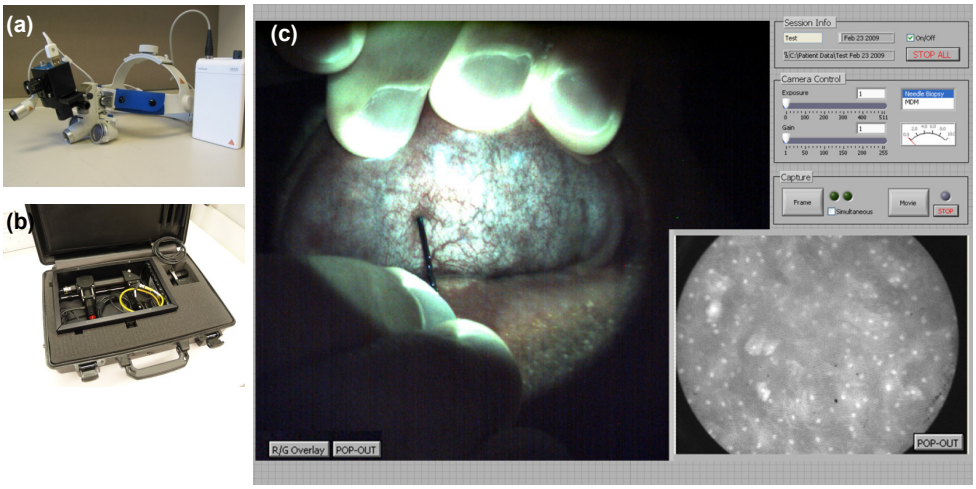


Figure 1: Combined portable widefield and high-resolution imaging systems. (A) The portable screening system weighs only 3 lb. (B) High-resolution microendoscope contained in a briefcase. (C) Widefield and high-resolution images of normal human oral mucosa acquired with the multimodal imaging system. In the widefield image (left frame), the green autofluorescence of normal tissue is apparent, as well as the microvascular network. The high-resolution fiber-optic probe can be seen in contact with the mucosal surface, approaching from the base of the widefield frame. The high-resolution image, acquired simultaneously, is displayed in the lower right frame, with the 800 μm diameter field-of-view corresponding to the tissue located beneath the tip of the fiber-optic probe. Following topical application of 0.05% proflavine solution to the probe tip, nuclei appear as discrete bright regions within each epithelial cell.

TD-T

Lateral-flow test for detection of cervical pre-cancer and cancer in low-resource settings – Johannes Schweizer

Berard-Bergery, M[1], Mahoney, CW[1], Silver, JE[1], Henry, P[1], Ho, M[1], Ramasamy, V[1], Tajan, E[1], Bisht, A[1], Jeronimo, J[2], Peck, RB[2], Weigl, BH[2], Gravitt, P[3], Howard, R[3], Castle, P[4], Lu, PS[1], and Schweizer, J[1]

[1]Arbor Vita Corporation, Sunnyvale, USA; [2]PATH, Seattle, USA; [3]Johns Hopkins Bloomberg School of Public Health, Baltimore, USA; [4]American Society for Clinical Pathology Institute, Washington, USA

Cervical cancer is one of the leading causes of cancer-related morbidity and mortality of women worldwide, with ~ 80% of the ~250,000 yearly worldwide deaths occurring in low-resource settings. If detected at the pre-cancer stage, clinical intervention is effective in preventing invasive cancer to develop. Implementation of broad screening programs for cervical neoplasia resulted in a striking decrease in cervical cancer mortality in many developed countries, underlining the impact of appropriate cervical cancer screening. The screening strategies used (Pap Test followed by colposcopy and biopsy of positives), however, are not appropriate for broad and effective use in limited resource settings, due to the overall low clinical sensitivity and specificity, and the need for complex infrastructure.

Arbor Vita Corporation, in collaboration with PATH, has developed the AV Avantage HPV-E6 Test (HPV E6 test) for detection of cervical pre-cancer and cancer in low-resource settings. The test detects elevated levels of the HPV-E6 oncoprotein. HPV-E6, in concert with HPV-E7, is a necessary causing agent for cervical high-grade pre-cancer and cancer to develop, and therefore the use of E6 as a marker would achieve high clinical sensitivity and specificity. The HPV E6 test promises therefore to identify those women who are in need of clinical follow-up among the many more women who have HPV infections without clinical consequences. The HPV E6 test uses the lateral-flow (strip-test) format, allowing for a simple and robust workflow (no complex equipment needed) and for stability of test storage (no cold chain required). The HPV E6 test's potential for high clinical specificity has been demonstrated in clinical pilot studies, and the test is currently taking part in a large clinical validation study in China (START-UP), developed by PATH and the Chinese Academy of Medical Sciences.

An overview presentation on principle and workflow of the HPV E6 test, and on data from the clinical pilot studies will be given.

TD-U

Microfluidics for global health diagnostics – Samuel Sia

Samuel Sia

Lab-on-a-chip (LOC) devices have a tremendous potential for improving the health of people in developing countries by providing immediate diagnosis in the field. The development of diagnostics for global health, however, presents unique and challenging design criteria. We will discuss our lab's current efforts, in conjunction with partners in industry, public health, and local governments, to develop new rapid diagnostic tests. Our tests span a variety of technologies, and target HIV, sexually transmitted diseases, and other infectious diseases.

Polymer-Based Modular Microfluidic Point-of-Care System for Automated Genotyping – Steven Soper

Steven A. Soper,[a,b,c] Mateusz L. Hupert,[a] Hong Wang,[a] Hui-wen Chen,[b] Donald Patterson,[a,e] Małgorzata A. Witek,[a,b] Proyag Datta,[d] Jost Gottert,[d] Michael C. Murphy,[a,c]

[a]Center for Bio-Modular Multi-Scale Systems (CBM^2), [b]Department of Chemistry, [c]Department of Mechanical Engineering, [d]Center for Advanced Microstructures and Devices (CAMD), [e]Louisiana State University, Baton Rouge, LA 70803, USA

Integration of the sample processing pipeline into a single system is of interest for point-of-care (POC) applications in the area of *in vitro* diagnostics, especially in 3rd world countries where resources are limited both from an infrastructure perspective and access to trained personnel. Microfluidics is a promising technology platform for POC applications as it can provide automated sample handling and reagent delivery as well as timely results with minimal operator intervention. We will discuss a microfluidic system for DNA analyses capable of detecting single nucleotide polymorphisms (SNPs) in a package incorporating all of the instrument peripherals that can accept a variety of clinical samples and search for the presence of mutations in genomic DNA that can provide important diagnostic information. Genomic DNA processing is carried out using a modular, polymer microfluidic, which consists of operational steps for cell sorting, cell lysis, solid-phase extraction of DNA, PCR amplification, discrimination reactions for identifying SNPs and readout using a low-density universal and programmable microarray. The microfluidic is manufactured as a 3-dimensional stack of 2 modules interfaced to a fluidic motherboard; a polycarbonate, PC, module used for solid-phase extraction and a poly(methyl methacrylate), PMMA, module used for detection of ligation products fitted with a monolithic laser coupling prism and air-embedded waveguide. The fluidic motherboard was made from PC and consisted of units for cell lysis, PCR, and a ligase detection reaction (LDR). As an application example, we will present results for the detection of point mutations in *BRCAI* genes. To further simplify the support peripherals, the laser-induced fluorescence detector could be eliminated by using LDR primers bearing gold nanoparticles; when silver stained, successful hybridization results could be read out using a digital camera. Results could be secured in <30 min compared to >12 h using conventional bench-top instrumentation. Due to the techniques used to fabricate the microfluidic system enabled by the substrate material choice, it can be manufactured and assembled in a high production mode at low-cost (<$10 per chip). In addition, modules can be added to the fluidic motherboard to expand the system's capabilities. For example, we have developed PMMA modules for selecting circulating tumor cells (CTCs), which will allow for the automated genotyping of selected CTCs in a variety of settings.

TD-W

Rapid and Efficient Isolation of Circulating Tumor Cells Using High Porosity Precision Microfilters – Cha-Mei Tang

Daniel Adams, Olga Makarova, Peixuan Zhu, Shuhong Li, Platte Amstutz, Cha-Mei Tang

Creatv MicroTech, Inc., Potomac, MD 20854

Background: We present a novel precision microfilter, CellSieve™, which achieves rapid and highly efficient isolation of circulating tumor cells (CTCs) from peripheral blood. Isolation of CTCs by size exclusion is a widely researched technique with the advantage of capturing cells without reliance on cell surface expression markers. For many years CTC filtration technology has relied on track-etch microfilters with randomly located pores and low-porosity. We have developed a new method of fabricating precision, high porosity microfilters that are strong, clear, and non-fluorescent.

Materials and Methods: We describe an assay to capture and enumerate both fixed and unfixed cancer cells on CellSieve™ microfilters. CellSieve™ microfilters are produced with 8 μm diameter pores in a clear polymer, with approximately 90,000 pores contained within a standard diameter, 13 mm filter. Breast cancer cell line, MCF-7, was used to evaluate filter performance. For fixed cancer cell assays, MCF-7 was pre-stained with acridine orange and DAPI dilacetate. Cells were individually counted (to obtain exact inputs), spiked into 7.5 mL whole human blood premixed with 7.5 mL of a fixation solution. Filtration was performed using filters mounted in a filter holder with the sample drawn by negative pressure at a flow rate of ~10 mL/min. The microfilter was removed from the holder and mounted onto a microscope slide, and filter-captured cells were counted using a fluorescence microscope under TRITC, FITC and DAPI settings. The procedure was then repeated using 7.5 mL PBS in place of the fixation solution diluted into whole blood. Both unfixed and fixed cell isolation by microfiltration were performed in triplicate.

Results: Precision CellSieve™ microfilters were able to capture MCF-7 spiked into 7.5 mL human blood with an efficiency of 98±2% for fixed cells, and 85±3% for unfixed cells. By contrast, track-etched microfilters captured only 73%±10% of fixed cells and 50±14% for unfixed cells. Blood cell contamination on the CellSieve™ filter ranges from 500 to a few thousand, < 0.00001% from the original 7.5 ml of whole blood, for blood collected within 24 hours of testing.

Conclusions: Microfiltration using CellSieve™ microfilters is a simple method to isolate circulating tumor cells from large volumes of whole human blood. This method can be done in less than 2 minutes with consistently high capture efficiency, while retaining a low rate of blood cell contamination.

Isolation and enrichment of cancer cells – Guren Wang

Guren Wang[1,2,*], Fang. Yang[1], Xiaoming. Yang[3], Mohammed. ALshreef[2], Nick. Metrakos[2], Eva. Juarez-Perez[2], Hong Jiang[4]

[1]Department of Mechanical Engineering; [2]Biomedical Engineering Program, University of South Carolina; [3]WJB Dorn Veterans Affairs Medical Center, Columbia, SC; Dorn Research Institute, Columbia, SC; [4]GraceFlow Technology, Irmo, SC *Corresponding author

Isolation and enrichment of cancer cells from other cells could significantly enhance sensitivity and specificity of cancer detection, since the cancer cell number is limited for early cancer diagnosis. Although there have been many publications on the cancer cell separation from other cells, one type cancer cell separation and isolation from other type cancer cells is yet to be investigated. Separation of different cancer cells is important in detecting circulating tumor cells. However, separation of different cancer cells is difficult, since they have similar size and are mostly epithelial cells. We use dielectrophoresis (DEP) in a microfluidics platform to study isolation and enrichment of cancer cell lines, such as colorectal cancer cell HCT-116, prostate cancer cell LNCap and breast cancer cell MCF-7 respectively. It is found that HCT-116 can be separated from normal Human Embryonic Kidney 293 cells (HEK-293). It is also found that LNCap and MCF-7 can be separated from HCT-116 respectively under different conditions, i.e. AC frequencies. Such a capability demonstrates the high specificity of DEP for cell isolation and separation, and could provide new biomarkers. Furthermore, to increase purity and throughput of the DEP separation, cascade and staggered DEP sorters are developed respectively. Particle and cell separation indicates that the cascade DEP cell sorter can significantly enhance the purity of the targeted cells for diagnostics; The staggered DEP sorter can largely increase sample throughput without compromising the purity to overcome the common issue related to microfluidic device. The results could provide a new opportunity for sample preparation in early cancer diagnosis.

Acknowledgements: It was also partially supported by NIH Grant Number RR 017698 and P20 RR-016461 respectively from the National Center for Research Resources.

Quantum dots and Microfluidics for Rapid Screening of Cell-Free DNA Biomarkers – Tza Huei (Jeff) Wang

Tza-Huei (Jeff) Wang

Departments of Mechanical Engineering & Biomedical Engineering, Sidney Kimmel Comprehensive Cancer Center, Institute of NanoBioTechnology, Johns Hopkins University

Tumorigenesis is a multi-step process resulting from gain-of-function (oncogenes) or loss-of-function (tumor suppressor) alterations, occurring through genetic or epigenetic abnormalities. Studies of these molecular aberrations such as point mutations, gene amplifications, DNA methylation can facilitate discovery of molecular biomarkers that aid in cancer detection and management. Circulating cell-free DNA consist of extra-cellular genetic material freely found in human body fluids such as serum, urine and sputum. Thus, cell-free DNA can be used to non-invasively determine the status of remote tumors by decoding the contained genetic and epigenetic information, potentially bypassing the need for tissue biopsies and more expensive imaging-based diagnostics. Whereas, the ability to detect specific genomic aberrations in bodily fluid represents a greater challenge, due to the small amounts of cell-free DNA available in these samples and the limited tumor content of such samples.

We develop a highly sensitive biosensor based on quantum dots (QD) to tackle the challenge of detecting rare cell-free DNA cancer markers. QDs make excellent donors to pair with organic dyes in the fluorescence resonance energy transfer (FRET) process due to the features of narrow emission spectra and small Stokes shift. This enables FRET with minimal direct acceptor excitation and donor-acceptor crosstalk, thereby permitting the design of FRET molecular sensors with extremely low intrinsic fluorescence backgrounds necessary for detecting biomolecular targets at low abundance. A point mutation assay is developed by incorporating QDs into DNA ligation reactions, facilitating highly sensitive and specific mutation detection in a simplified homogeneous format. This mutation nanoassay has been exemplified with detection of Kras point mutations in clinical samples from patients with ovarian serous borderline tumors (SBTs). In addition, a DNA methylation assay called MS-qFRET is developed based on QD-FRET. This approach detects as little as 15 pg of methylated DNA in the presence of a 10,000-fold excess of unmethylated alleles and allowed for multiplexed analyses. The high sensitivity of MS-qFRET enabled one-step detection of promoter methylation of multiple tumor suppressor genes in patient serum and sputum samples that contained low concentrations of methylated DNA, which normally would require a nested PCR approach. The direct application of QD nanoassays on clinical samples offers great promise for its translational use in early cancer diagnosis, prognostic assessment of tumor behavior, as well as monitoring response to therapeutic agents.

Although analysis of cell-free DNA offers a highly sensitive and noninvasive approach for cancer detection, current applications are limited to highly regulated and maintained central laboratories. Being able to perform molecular diagnostics at the point of care (POC) in a resource-scarce environment is crucial for global health in combating cancer. Toward this end, we have been developing a droplet microfluidic, sample-to-answer platform for molecular diagnostics. This platform enables the integration of sample preparation and genetic analysis within discrete droplets, including the steps of cell lysis, DNA binding, washing, elution, amplification and detection. The microfluidic device was self contained, with all reagents stored in droplets, thereby eliminating the need for fluidic coupling to external reagent reservoirs. Feasibility of the platform was demonstrated by analyzing ovarian cancer biomarker Rsf-1 in blood samples with the real time polymerase chain reaction and the real time helicase dependent amplification.

Bench Top and Handheld Magneto-Nanosensor Platform for Multivariate In Vitro Diagnostics of Cancer – Shan X. Wang

Shan X. Wang

Professor of Materials Science & Eng., and of Electrical Engineering, and by courtesy of Radiology, Stanford University

Reproducible and multiplex protein assays are greatly desired by cancer biologists as well as clinical oncologists to rapidly follow numerous proteins in clinical samples. We have now successfully applied magneto-nano biochips based on giant magnetoresistance (GMR) spin valve sensor arrays and magnetic nanoparticle labels (nanotags) to the detection of biological events in the form of multiplex protein assays (4-to 64-plex) with great speed (30 min. 2 hours), sensitivity (1 picogram/milliliter concentration levels or below), selectivity, and economy [1-3]. More recently, we achieved the first demonstration of a nanolabel-based technology capable of rapidly isolating cross-reactive antibody binding events in a highly multiplex manner. By combining magnetic nanotechnology with immunology, we have devised an easy to use and rapid auto-assembly assay which is ideal for high-density screens of aberrant protein binding events and for quantitative and multiplexed measurements of binding kinetics [4-5]. Furthermore, we have developed the auto-assembly assay for disease biomarker detection which obviates the need for washing steps and is run on a handheld sensing platform. By coupling magnetic nanotechnology with an array of magnetically responsive nanosensors, we demonstrate a rapid, multiplex immunoassay that eliminates the need for trained technicians to run molecular diagnostic tests. Furthermore, the platform is battery-powered and ultraportable, allowing the assay to be run anywhere in the world by any individual [6]. References: [1] Gaster RS, Hall DA, et al., Nature Medicine, 15, 1327-1332, 2009. [2] Osterfeld SJ, Yu H, et al., PNAS, 105, 20637-20640, 2008. [3] Hall DA, Gaster RS, et al., Biosensors and Bioelectron., 25, 2051-2057, 2010. [4] Gaster RS, Hall DA, Wang SX, Nano Letters, published online, DOI: 10.1021/nl1026056. [5] Gaster RS et al., Nature Nanotechnology, 6, 314-320, 2011. [6] Gaster RS, Hall DA, Wang SX, Lab on a Chip, 11 (5), 950 - 956, 2011.

This work was supported in part by National Cancer Institute Grants U54CA119367, U54CA143907, and U54CA151459. Additional funding comes from Gates Global Challenge Exploration Award, Stanford Medical School MSTP program, National Semiconductor Corporation and the Achievement Rewards for College Scientists (ARCS) foundation.

TD-AA

Innovative Membrane Microfilter Device for Tumor Cell Capture and Analysis in Resource-Limited Settings – Anthony Williams

Anthony Williams[1], Ram Datar[1], Yu-Chong Tai[2], and Richard Cote[1]

[1]Department of Pathology, University of Miami-Miller School of Medicine, Miami, Florida; [2]Department of Electrical Engineering, California Institute of Technology, Pasadena, California

Metastasis, the most important determinant in the management of cancer, accounts for >90% of patient mortality. Clinical guidelines of post-treatment patient surveillance often require frequent and long-term follow up accompanied with expensive, invasive and sometimes inefficient techniques. Detecting the rare circulating tumor cells (CTC) has emerged as a means of providing a more efficient and non-invasive approach to detect early evidence of metastasis and enable therapeutic monitoring. While numerous technologies (most immunoaffinity-based) have been developed in recent years to isolate CTC, difficulties with sensitivity, specificity, efficiency, and high costs of these assays have limited their clinical translation. We developed a novel membrane microfilter device to enrich and capture CTC directly from patient blood. This platform has a superior sensitivity and efficiency as seen in published head-to-head comparison with the CellSearch® platform. Owing to its open-format, beyond enumeration, the microfilter also allows for CTC characterization by techniques such as multi-marker immunofluorescence, FISH, PCR and CGH. Our cell-size-based approach, in contrast to immunoaffinity-based platforms, is 'antigen expression-agnostic'; allowing analysis of even tumor types lacking target antigens. The microfilter also has a potential to capture and analyze tumor cells from other body fluids such as urine, plural effusions, cerebrospinal fluid and ascites. Portability, low production cost, easy uniformity and reproducibility in manufacture, and rapid sample processing are unique characteristics of the microfilter device. For rural and underserved communities where blood samples must otherwise be sent to distant, centralized laboratories for analysis, the microfilter can be used as a point-of-care alternative platform, and has the transformative potential to provide a cheaper and easier alternative with significantly rapid turn-around time for CTC isolation. With the ability to perform multiple, repeated sample analyses to detect recurrent disease early and enable therapeutic monitoring, the microfilter can revolutionize the patient management, and improve health care delivery globally.

TD-BB

Using portable glucose meters for low-cost quantification of various non-glucose analytes related to health and environment – Yu Xiang

Yu Xiang and Yi Lu*

Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA

Developing simple methods for the point-of-need detections of multiple critical analytes in relevant self-collected biospecimens is of significant importance in acquiring essential information within a short timeframe to guide an immediate clinical action under limited resource conditions. Although many clinic diagnosis methods are available as laboratory-based tests, few of them can be readily applied for the point-of-need detections by unskilled users with limited resources. One of the most successfully developed and commercialized devices for point-of-need diagnosis is the blood glucose meter (BGM). The BGM can be operated by the public with limited resources and no professional skills, and has either saved or improved the quality of millions diabetic patients lives worldwide. BGM tests are now very simple, low-cost, and reliable. Currently, BGMs are also integrated into cell phones for an even wider base of users. However, BGMs can only be used by the diabetic patients to detect a single target of glucose in a single specimen of blood. We have developed a novel technology that takes the advantages of well-developed, widely available BGMs for simple point-of-need detections of a broad range of critical analytes for the public in limited resource settings. The technology linked BGMs with functional DNAs and antibodies to realized the detections of a broad range of non-glucose targets related to health and environment by a glucose meter, such as heavy metal ions (lead and uranium), small molecules (cocaine, ochratoxin A and adenosine) and biomolecules (interferon-gamma, prostate specific antigen and nucleic acids). The concentration of target was successfully transformed into that of glucose for glucose meter detection, through invertase-catalyzed hydrolysis of sucrose.

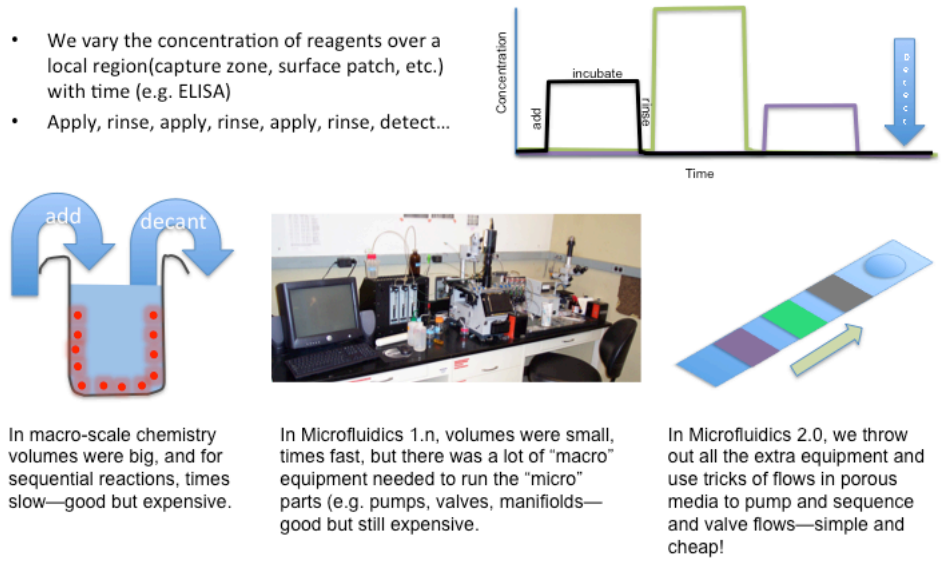
We wish to thank the National Institutes of Health (ES16865), U.S. Department of Energy (DE-FG02-08ER64568), and National Science Foundation (CTS-0120978) for financial support

Microfluidics 2.0: Dropping the Costs for Diagnostic Tests and Screening – Paul Yager

Elain Fu, and Barry Lutz, and Paul Yager

Department of Bioengineering, University of Washington, Seattle, WA

When Microfluidics exploded in the 1990's, its main aim was to move from the discrete processing of fluids from container to container using manual pipettes or robots, to *integration* of the processes into monolithic devices. Microfluidics did that, and more, but at a cost---there were still pumps and pressure sources and valves needed to push the fluids around, and those things generally were big, expensive, and lived off the chip. Microfluidics 1.n systems are still, largely, in the big well-equipped labs.



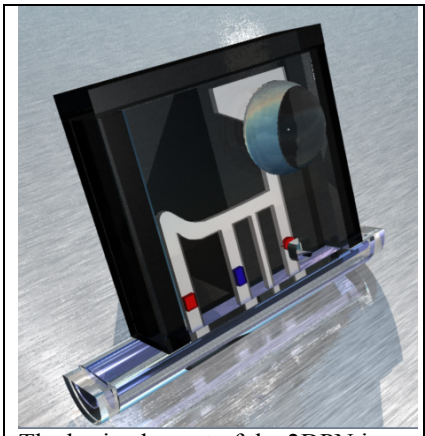
ELISA is still the best way to measure the concentrations of biomarkers. In ELISA, the approach is to cause sequential changes in reagent concentrations over a specific zone covered with capture molecules. The new capability in the two-dimensional paper networks used in Microfluidics 2.0 is the ability to sequence reagents at predictable concentrations for predictable times over multiple capture sites; this combines the best features of lateral flow tests with the best of "conventional" microfluidics.

By returning to what we've known for decades about moving fluids without pumps or valves in porous media, Microfluidics 2.0 offers us a chance to get the hoped-for advantages of microfluidics, but without the expense. Microfluidics 2.0 has the power to make sophisticated chemical and biochemical measurements much simpler, *and (a lot) cheaper*. By piggybacking on the revolution in information technologies, we can move the data generated anywhere in almost no time.

Technologies arising from Microfluidics 2.0 will:

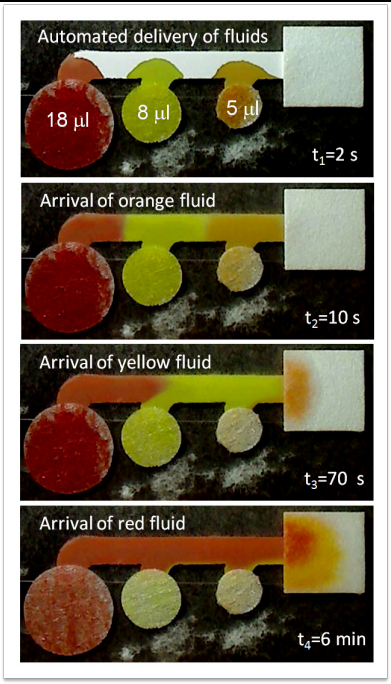
- Allow quantitative measurement of small molecules, large proteins and nucleic acids at low concentrations in biological fluids rapidly and by anyone.
- Allow minimally trained personnel to perform chemical and biochemical analyses when and where they are needed.
- Reduce the cost of healthcare in the developed world by commoditizing a wide range of diagnostic tests (as has been done for blood glucose testing) to the point where early and frequent screening for disease is economical, voluntary and ubiquitous
- Bring sophisticated medical and agricultural diagnostics to low-resource settings—e.g., places in the developing world without the funds or infrastructure.

Some simple one-dimensional porous devices have been used in research tools and commercial products for decades (e.g., paper chromatography and lateral flow immunoassays). New and much more sophisticated devices and systems are now made possible by forming porous materials in complex shapes in 2 and 3 dimensions. Because fluid flow can be controlled precisely without the need for either positive displacement of pressure-driven pumps, the movement of the fluids (sample and all the reagents) is *programmed* by the structure of simple, inexpensive, single-use pieces of paper. Just add the sample, and perhaps some water, and the paper does the rest.

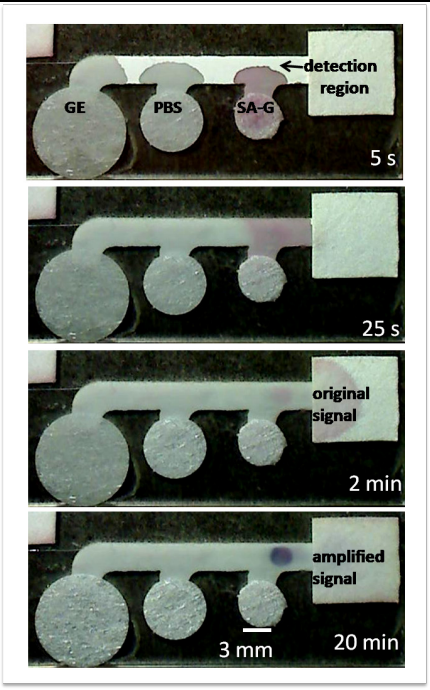


The basic element of the 2DPN is the ability to sequence different chemicals by programming the size and shape of the paper network. Shown is a conceptual 2DPN activated by adding water to a single trough at the bottom.

This 2DPN is a "monopapyric" paper circuit activated by addition of water; color changes in capture spots. There are two ways to activate the 2DPNs. This version is activated by wetting the bottom of the strips, which then suck up fluid and rehydrate multiple reagents; reagents are delivered sequentially as determined by the device geometry.



An alternative way to activate 2DPNs is to fold wetted pads onto an existing paper network (microfluidic origami). By filling the pads with wet reagents (or rehydrating dry reagents stored in each pad), the circuit is formed and the 2DPN delivers precise reagents to specific portions of the network near the wicking pad.



A simple demonstration of Increasing the sensitivity of the lateral flow immunoassay format by automating processing steps for chemical signal amplification in a simple 2DPN. Amplification by adding Au to captured Au nanoparticles (at right) results in a significantly darkened optical detection signal.

Characteristics of existing RDTs and the proposed multiplexed 2DPN rapid diagnostic tests

Characteristics	Conventional RDTs	2DPN rapid diagnostic
Sensitivity	Considered poor in many cases	Exceed existing RDTs by using chemical amplification of detection spots
Specificity	Adequate	Meet or exceed existing RDTs
Time	Less than 20 min	Less than 20 min
Training	Easy to use by untrained operators (CLIA waived to CLIA moderate)	Easy to use by untrained operators (goal: CLIA waived status)
Readout	Visible signal read by eye	Visible signal read by eye or quantified with a cell phone camera
Cost	Less than $1	Less than $1
Intended setting	Point-of-care	Point-of-care: physician's office or hospital ER
Sample conditioning	No	Yes—complex multistep processing possible
Multiplexable	Yes, but limited to ~4 capture lines	Highly
Adaptable	Yes	Yes, can be used generally for antigen detection (e.g. viral infections, bacterial infections, toxins)

A smart fiber optic sensor for detection of oral and cervical cancer in developing world – Bing Yu

Bing Yu[1]*, Vivide Chang[1], Amy Shah[1], Delson Merisier[2], David Walmer[2,3], and Nirmala Ramanujam[1]

[1]Department of Biomedical Engineering, Duke University, Box 90281, Durham, NC 27708, USA; [2]Family Health Ministries, Leogane, Haiti; [3]Department of Gynecology and Obstetrics, Duke University Medical Center, Box 3084, Durham, NC * Email: bing.yu@duke.edu

Each year, over 481,000 new cases of oral cancer are diagnosed worldwide, with a 5-year mortality of ~50% and nearly two-thirds of which occurs in developing world. Cervical cancer is the second most common cancer in women with an incidence and death rate of 16 and 9 per 100,000 women, respectively, and 80% of cases occur in the developing world. The high death rate in developing countries is largely due to the fact that these countries do not have the appropriate infrastructure and resources to support the organized screening and diagnostic programs that are available in the U.S.

The optical absorption and scattering properties of epithelial tissues reflect their underlying physiological and morphological properties. Diffuse reflectance spectroscopy (DRS) with a fiber optic probe can be used to noninvasively quantify these tissue properties and has shown promise for diagnosis of early precancerous changes in the cervix and oral cavity by our group as well as others. However, current DRS techniques are susceptible to several sources of systematic and random errors, such as uncontrolled probe-to-tissue interface and lack of a real-time calibration that can influence the robustness of this technology in resource-poor settings. These systems also use bulky, high power and expensive optical components, such as thermal light sources, spectrographs, and cooled CCD cameras, which need a stable power supply.

In this technology demonstration, we present a portable, easy-to-use and low cost, yet accurate and reliable DRS device that can aid in the screening and diagnosis of oral and cervical cancer at an early stage and that is well suited for use in a low-resource setting. The device uses an innovative smart fiber-optic probe to eliminate operator bias, state-of-the-art photonics components to reduce power consumption, and automated software to reduce the need of operator training.

Global Health Research Programs and the National Cancer Institute's Research Programs and Funding Opportunities

DIVISION OF CANCER TREATMENT AND DIAGNOSIS (DCTD)
THE CANCER DIAGNOSIS PROGRAM (CDP)

The Cancer Diagnosis Program (CDP) strives to improve patient outcomes by effectively moving new diagnostic tools into clinical practice. The program stimulates, coordinates, and funds resources and research on diagnostics and improved technologies to better characterize cancers in order to develop information that can aid cancer patients and their physicians in clinical decision making.

CDP is active in three areas:

- ***Diagnostic Biomarkers and Technology***

  Incorporation of new knowledge of cancer biology into markers/assays useful for treatment decision making

  Development of new technologies and devices for cancer diagnostics

  Integration of results from biomarker research for use in cancer diagnostics

- ***Resources Development:***

  Development and supports human specimen resources

  Assistance for researchers in locating and gaining access to the specimens from cancer patients

  Stimulation of research on sample preparation technologies

- ***Diagnostics Evaluation***

  Development of prognostic and predictive markers/assays for cancer

  Validation studies of markers/assays

  Support and assistance for prospective correlative studies in treatment protocols

For more information: http://www.cancerdiagnosis.nci.nih.gov/

FUNDING OPPORTUNITIES IN CANCER DIAGNOSIS

The full text of these announcements can be found in the NIH Guide for Grants and Contracts at http://grants.nih.gov/grants/guide/index.html.

Development, Application, and Evaluation of Prediction Models for Cancer Risk and Prognosis: PA-10-025 (R01) & PA-10-026 (R21)
Release/Posted Date: November 16, 2009; Expiration Date: January 8, 2013
Application Receipt Dates: February 5, June 5 & October 5 (R01) & February 16, June 16, October 16 (R21)
The NCI Division of Cancer Control and Population Sciences (DCCPS) and the Division of Cancer Treatment and Diagnosis (DCTD) encourage application submissions for research projects that will develop, apply, and evaluate new and existing cancer risk and prognostic prediction models for use by researchers, clinicians, and the general public. The purpose of this Funding Opportunity Announcement (FOA) is to encourage clinicians, epidemiologists, geneticists, statisticians, and translational researchers working in the fields of cancer control, prevention and treatment to improve existing models for cancer risk and prognosis by developing innovative research projects that use existing data; develop new models for cancer risk and prognosis; and validate new models and evaluate their utility in research and clinic settings. Applications that are focused on the identification and characterization of prognostic/diagnostic markers are NOT responsive to this FOA. Contact: Dr. J. Milburn Jessup, DCTD, 301-435-9010, E-mail: jessupj@mail.nih.gov, Dr. Andrew N. Freedman, DCCPS, 301-435-6819, E-mail: freedmaa@mail.nih.gov, or Dr. Mukesh Verma, DCCPS, 301-594-7344, E-mail: vermam@mail.nih.gov

Exploratory Studies in Cancer Detection, Diagnosis and Prognosis: PA-08-267 (R21)
Release/Posted Date: September 23, 2008; Expiration Date: September 8, 2012
Application Receipt Dates: February 16, June 16, October 16

Developmental Research in Cancer Prognosis and Prediction: PA-09-158 (R21) & PA-09-159(R33)
Release/Posted Date: April 14, 2009; Expiration Date: May 8, 2012
Application Receipt Dates: February 16, June 16, October 16. The Cancer Diagnosis Program invites applications for research projects to evaluate the utility and pilot the application of new strategies for determining cancer prognosis or predicting response to therapy. This program provides support for a first phase award for technical development. Contact: Dr. Tracy Lively, 301-496-1591, E-mail: livelyt@mail.nih.gov; Dr. Magdalena Thurin, 301-496-1591, E-mail: thurinm@mail.nih.gov; Dr. James V. Tricoli, 301-496-1591, E-mail: tricolij@mail.nih.gov; Dr. John M. Jessup, (301)496-1591, E-mail: jessupj@mail.nih.gov.

Pilot Studies in Pancreatic Cancer: PA-08-208 (R21) & PA-08-209 (R03)
Release/Posted Date: July 18, 2008; Expiration Date: Sep 8, 2011
Application Receipt Dates: February 16, June 16, October 16.
This PA aims to promote innovative research across multiple disciplines to better understand the etiology of pancreatic cancer and to facilitate its early detection, prevention, and treatment. Proposed projects may center on the biology, etiology, detection, prevention, and treatment of pancreatic cancer. This FOA focuses on pilot projects in early and conceptual stages that could provide a basis for more extended research. Contact: Dr.Mukesh Verma, Division of Cancer Control and Population Science, (301) 594-7344, E-mail: vermam@mail.nih.gov; Dr.William C. Timmer Division of Cancer Treatment and Diagnosis, 301-496-8866, E-mail: timmerw@mail.nih.gov

Biomarkers of Infection-Associated Cancers: PA-11-158(R01) & PA-11-159(R21) (Reissue of PA-08-156 & PA-08-157)
Release/Posted Date: April 22, 2008; Expiration Date: May 8, 2014
Application Receipt Dates: February 16, June 16, October 16 (R21) & February 5, June 5, October 5 (R01)

Exfoliated Cells and Circulating DNA in Cancer Detection and Diagnosis: PA-09-238 (R21)
Release Date: July 22, 2009; Expiration Date: September 8, 2012
Application Receipt Dates: March 16, July 16, November 16

Correlative Studies with Specimens from Multi-Site Trials: PA-08-134 (R01) & PA-08-133(R21)
Release/Posted Date: April 4, 2008; Expiration Date: (R01) May 8, 2012; (R21) May 8, 2011 (will be reissued)
Application Receipt Dates (R01): February 5, June 5, October 5 (R01) & February 16, June 16, October 16 (R21)The Cancer Therapy Evaluation Program (CTEP) and Cancer Diagnosis Program (CDP) of the Division of Cancer Treatment and Diagnosis and the Cancer Biomarkers Research Group of the Division of Cancer Prevention, NCI invite research grant applications (R01 or R21) from institutions or consortia to perform translational research on correlations between biologic features of tissue specimens collected from the NCI Clinical Trials Cooperative Groups or other large multi-institutional clinical trials and patient outcomes. Contact: Dr. Magdalena Thurin, Cancer Diagnosis Program, 301-496-1591, E-mail: thurinm@mail.nih.gov or Dr. Roy Wu, Cancer Therapy Evaluation Program, 301-496-8866, E-mail: Wur@mail.nih.gov

Strategic Partnering to Evaluate Cancer Signatures [SPECS II]:PAR-11-151(U01) (Reissue of PAR-10-126)
Release Date: March 8, 2010; Expiration Date: June 16, 2012
Application Receipt Dates: June 15, 2011; June 15, 2012This Funding Opportunity Announcement (FOA), issued by the National Cancer Institute (NCI) of the National Institutes of Health (NIH), encourages the submission of grant applications for support of the clinical application of multi-analyte molecular signatures derived from comprehensive molecular annotation of tumors. The NCI invites investigators to form strategic partnerships that will bring together the multi-disciplinary expertise and resources needed to determine how the information derived from comprehensive molecular analyses can be used to improve patient care and, ultimately, patient outcomes. Contact: Dr. Tracy Lively, 301-496-1591, E-mail: livelyt@mail.nih.gov; Dr. James V. Tricoli, 301-496-1591, E-mail: tricolij@mail.nih.gov

Bioengineering Technologies: The NIH bioengineering program supports basic, applied, and translational bioengineering research that addresses important biological or medical research problems. CDP Contact: Dr. Avraham Rasooly; 301-496-8639; E-mail, rasoolya@mail.nih.gov

The NCI Innovative Molecular Analysis Technologies (IMAT) Program (http://innovation.cancer.gov/).
Release/Posted Date: October 26, 2009; Expiration Date: October 1, 2010 (will be reissued)
Application Due Date(s): February 23, 2010; May 27, 2010; September 30, 2010

FOR THE LATEST INFORMATION ABOUT NCI INITIATIVES, VISIT

Division of Extramural Activities, National Cancer Institutehttp://deainfo.nci.nih.gov/funding.htm

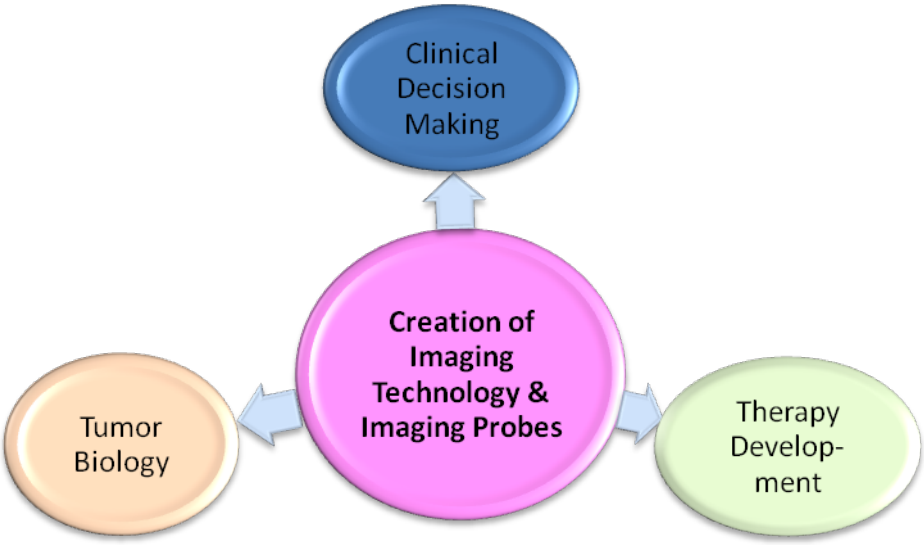
DIVISION OF CANCER TREATMENT AND DIAGNOSIS (DCTD)

THE CANCER IMAGING PROGRAM

The Cancer Imaging Program (CIP) of the Division of Cancer Treatment and Diagnosis (DCTD) is an innovative program that encourages coordination and collaboration among experts in basic, translational, and clinical research to advance the understanding of cancer through imaging and to create better diagnosis and treatment options for patients.

The role of imaging in cancer research is changing, and CIP continues to be a catalyst for this transformation. In the past, the focus of imaging research was creating clearer and more detailed anatomic pictures of organs and tissues. Today, the primary new thrust in imaging is on functional or molecular imaging, which visualizes the physiological, cellular, or molecular processes in living tissues as they take place. Molecular imaging is critical for fundamental improvements in the care of cancer patients. While we continue to discover new molecular signatures of cancer in our crusade to develop more effective therapies with lower morbidity, these efforts can be successful only through understanding how these targets integrate into the complex systems of tumor biology. *In vivo* molecular imaging is a unique method to allow us to acquire this knowledge by non-invasive visualization of the entire organism.

In the next decade, CIP-sponsored research will not only contribute to the basic understanding of various cancers, but it will enhance the clinical role of imaging in noninvasive diagnosis, help identify disease subsets in patients, improve disease staging and treatment monitoring, and play a pivotal role in the development of new therapies.



CIP unites researchers from disciplines as diverse as radiology, nuclear medicine, bioengineering, biology, chemistry, computer science, and physics in a team approach to problem solving. The program encourages extramural researchers to integrate and apply new imaging discoveries and developments to drug discovery, monitoring of therapies, and understanding cancer biology. This is all directly aimed at the clinical management of cancer and cancer risk. CIP divides its staff and administered grants among four areas:

- Clinical Trials
- Molecular Imaging
- Image-Guided Intervention
- Imaging Technology Development

Through this organization, CIP supports and advises innovative investigators in academia and private industry as they create and apply to human disease the next generation of imaging technologies, including molecular probes, imaging devices, new contrast agents and image guided therapies.

As part of its cutting-edge program, CIP plays a critical role in the activities of the NIH and the NCI contributing to the integration of imaging with emerging technologies such as nanotechnology, proteomics, and high-throughput screening. In addition to funding projects in key areas, CIP supports researchers by providing pooled resources and developing protocols that encourage the sharing of data, samples, and results.

Current Funding Initiatives from CIP:

Academic-Industrial Partnerships for Development and Validation of In Vivo Imaging Systems and Methods for Cancer Investigations (R01) (PAR-10-169)
Application Receipt Date(s): Multiple dates, see announcement.
Expiration Date: May 8, 2013
Contacts: Houston Baker, Ph.D., Tel 301-496-9531, e-mail bakerhou@mail.nih.gov
James Deye, Ph.D., Tel 301-496-6111, e-mail deyej@mail.nih.gov

PAR-11-216: Early Phase Clinical Trials in Imaging and Image-Guided Interventions (R21)
Release Date: May 24, 2011
Application Receipt/Submission Date(s): July 27, 2011; November 10, 2011; March 13, 2012; July 11, 2012; November 13, 2012; March 13, 2013; July 11, 2013; November 13, 2013; March 13, 2014, by 5:00 PM local time of applicant organization.
Contact:Lalitha K. Shankar, M.D., Ph.D. NCI, Phone: 301-496-9531, (shankarl@mail.nih.gov)
Contact:Frank I. Lin, M.D., NCI, Phone: 301-496-9531, (frank.lin2@nih.gov)
For Image-Guided Intervention, contact: Keyvan Farahani, Ph.D. NCI, Phone: 301-496-9531, (farahank@mail.nih.gov) Expires March 14, 2014

PA-10-080 and PA-10-079: Image-Guided Interventions (STTR [R41/R42] & SBIR [R43/R44])
Release Date: January 8, 2010
Application Receipt/Submission Date(s): Multiple dates, see announcements.
Contacts: Keyvan Farahani, Ph.D. NCI, Phone: 301-496-9531, Email: farahank@mail.nih.gov
Contacts: David Beylin, M.S., NCI, Phone: 301-496-0079, Email: beylind@mail.nih.gov Expires January 8, 2013

PAR-11-150: Quantitative Imaging for Evaluation of Responses to Cancer Therapies (U01)
Release Date: March 14, 2011
Application Receipt Date(s): Standard dates
No set-aside
Contact: Robert J. Nordstrom, Ph.D. (nordstrr@mail.nih.gov) at 301-594-9121 Expiration Date: May 8, 2014

PA-09-253: Image-guided Drug Delivery in Cancer (R01)
Release Date: August 13, 2009
Application Receipt Date(s): Standard dates
No set-aside
Contact: Keyvan Farahani, Ph.D. (farahank@mail.nih.gov) at 301-451-2651 Expiration Date: May 8, 2013

PAR-09-157: In vivo Cellular and Molecular Imaging Centers (ICMICs) (P50)
Release Date: April 13, 2009
Letters of Intent Receipt Dates: September 28, 2009, September 28, 2010, September 28, 2011
Application Receipt Dates: October 28, 2009, October 28, 2010, October 28, 2011
Contact: Anne Menkens, Ph.D. (am187k@nih.gov) at 301-435-9024; Expiration Date: October 29, 2011

THE DIVISON OF CANCER PREVENTION (DCP)

The Division of Cancer Prevention (DCP) is the primary unit of the National Cancer Institute devoted to cancer prevention research. DCP provides funding and administrative support to clinical and laboratory researchers, multidisciplinary teams, and collaborative, research-based networks.

The Cancer Biomarkers Research Group encourages applications to develop technologies that are useful for pre-clinical cancer detection, prediction of progression from premalignant lesions to cancer, early cancer detection, and risk assessment. Technologies of interest include methods to improve biomarker discovery and multiplexing platforms to accurately measure low abundance markers, especially those that use body fluids or cells in these fluids. Also of interest are integrated technological platforms for enabling multiplexed biomarker assays, and cell imaging technologies to detect premalignant lesions. http://prevention.cancer.gov/programs-resources/groups/cb The Cancer Biomarkers Research Group administers the Early Detection Research Network and the Alliance for Glycobiologists for Detection of Cancer and Cancer Risk.

Early Detection Research Network (EDRN) is a consortium of laboratories and clinical centers to discover and validate biomarkers for assessment of cancer and cancer risk (http://edrn.nci.nih.gov/). EDRN provides a vertically integrated network of academic and industry-based scientists collaborating to meet the challenge of developing new cancer screening and early detection products. The mission of EDRN is both to implement strategic and systematic, evidence-based discovery, development, and validation of biomarkers to identify cancer risk, cancer, and cancer prognoses, and to coordinate biomarker research and therapeutic strategies in order to reduce cancer morbidity and mortality.
The EDRN Associate Membership Program is designed for investigators who are not affiliated with EDRN and wish to propose collaborative studies within the scope and objectives of the EDRN (http://edrn.nci.nih.gov/colops/assoc).

The Alliance of Glycobiologists for Detection of Cancer and Cancer Risk, a consortium of seven Tumor Glycomics Laboratories and research partners (http://glycomics.cancer.gov/). The mission of the Alliance is to study structure and function of glycans in relation to cancer development towards developing clinically useful biomarkers for the early detection of cancer by using a variety of approaches and technologies. This charge also requires extensive collaborations across institutions with different skills and facilities to accelerate glycan-based biomarkers to the forefront of NCI's efforts to detect and diagnose cancer at early stages.

Notice of Intent to Publish a Request for Applications for Alliance of Glycobiologists for Detection of Cancer and Cancer Risk: NOT-CA-11-013 The National Cancer Institute announces the intent to publish a Funding Opportunity Announcement (FOA) for research projects that elucidate how changes in carbohydrates promote cancer progression and use this information to identify glycan-based abnormalities with the potential to serve as biomarkers for early cancer detection or risk assessment. This planned Funding Opportunity Announcement (FOA), which will use the cooperative agreement funding instrument, is expected to be published in Summer 2011 with an application due date in the Fall of 2011.

For more information: http://prevention.cancer.gov/programs-resources/groups/cb

FUNDING OPPORTUNITIES IN CANCER PREVENTION AND EARLY DETECTION

The full text of these announcements can be found in the NIH Guide for Grants and Contracts at http://grants.nih.gov/grants/guide/index.html.

Exfoliated Cells and Circulating DNA in Cancer Detection and Diagnosis (R21) PA-09-238
Expiration Date: September 8, 2012
Purpose: Encourages applications to develop novel technologies for capturing, enriching, and preserving exfoliated abnormal tumor cells and macromolecules in body fluids or effusions and to develop methods for concentrating the content of such specimens that originated from tumor or a pre-neoplastic lesion for biomarker studies.

Exploratory Studies in Cancer Detection, Diagnosis and Prognosis (R21) PA-08-267
Expiration Date: September 8, 2012
Purpose: Encourages applications that involve the initial evaluation of new molecular or cellular characteristics of tumors, pre-malignant cells, or the development of assays that will be useful for cancer detection, diagnosis, and/or prognosis.

Identifying Non-coding RNA Targets for Cancer Early Detection and Prevention (R01) PA-09-199
Identifying Non-coding RNA Targets for Cancer Early Detection and Prevention (R21) PA-09-200
Expiration Date: September 8, 2012
Purpose: Encourages research grant applications on the discovery and characterization of non-coding RNAs in preneoplasias and early stage cancers to: 1) improve early cancer detection, intervention, and prevention; 2) predict risk of progression from preneoplasia to cancer, and 3) distinguish benign lesions from precancerous lesions.

Biomarkers for Early Detection of Hematopoietic Malignancies (R01) PA-09-197
Biomarkers for Early Detection of Hematopoietic Malignancies (R21) PA-09-197
Program Announcement (PA) Number: PA-09-197
Purpose: Encourages research grant applications for the development and validation of biomarkers for early detection, prediction of progression, and recurrence of hematopoietic malignancies, especially in high-risk individuals and for risk assessment of primary and secondary hematopoietic malignancies and for the development and improvement of specific technologies and methods for quantitative detection of novel biomarkers associated with hematopoietic malignancies.

Biomarkers of Infection-Associated Cancers (R01) PA-11-158
Program Announcement (PA) Number: PA-11-158
Biomarkers of Infection-Associated Cancers (R21) PA-11-159 Expiration Date: May 8, 2014
Purpose: Encourages applications (that propose to identify biomarkers for cancers where the etiology of the disease is attributed to infectious agents.

Mitochondria in Cancer Epidemiology, Detection, Diagnosis and Prognosis (R01) PA-11-073
Mitochondria in Cancer Epidemiology, Detection, Diagnosis and Prognosis (R21) PA-11-074
Expiration Date: January 8, 2014
Purpose: Encourage applications to develop and validate new mitochondrial-related biomarkers for cancer early detection, diagnosis, prognosis, risk assessment, and response to preventive and ameliorative treatments.

Cancer Prevention Research Small Grant Program (R03): PAR -11-079
Expiration Date: December 17, 2013
Purpose: The National Cancer Institute (NCI) invites applications that propose small and time-limited projects pertinent to the development of cancer chemoprevention agents, biomarkers for early cancer detection, cancer-related nutrition science, and/or clinical prevention studies that focus on specific target organs. Ultimately, these small grants are expected to facilitate the development of full research projects grants.

DIVISION OF CANCER CONTROL AND POPULATION SCIENCES (DCCPS)

EPIDEMIOLOGY AND GENETICS RESEARCH PROGRAM (EGRP)

EGRP focuses on methods to address epidemiologic data collection, study design and analysis, and to modify technological approaches developed in the context of other research endeavors for use as biomarkers and methods to understand cancer susceptibility. **For more information: http://epi.grants.cancer.gov/mtb/**

FUNDING OPPORTUNITIES IN CANCER EPIDEMIOLOGY

The full text of these announcements can be found in the NIH Guide for Grants and Contracts at http://grants.nih.gov/grants/guide/index.html.

Mitochondria in Cancer Epidemiology, Detection, Diagnosis, and Prognosis
Program Announcement PA-11-073 (http://grants.nih.gov/grants/guide/pa-files/PA-11-073.html)
Program Announcement PA-11-074 (http://grants.nih.gov/grants/guide/pa-files/PA-11-074.html)

Epigenetic Approaches in Cancer Epidemiology
Program Announcement PA-10-032 (http://grants.nih.gov/grants/guide/pa-files/PA-10-032.html)
Program Announcement PA-10-031 (http://grants.nih.gov/grants/guide/pa-files/PA-10-031.html)

Small Grant Program for Cancer Epidemiology
Program Announcement PA-08-237 (http://grants.nih.gov/grants/guide/pa-files/PAR-08-237.html)

Pilot Studies in Pancreatic Cancer
Program Announcement PA-08-208 (http://grants.nih.gov/grants/guide/pa-files/PA-08-208.html)
Program Announcement PA-08-209 (http://grants.nih.gov/grants/guide/pa-files/PA-08-209.html)

Risk Prediction Models in Cancer Epidemiology
Program Announcement PA-10-026 (http://grants.nih.gov/grants/guide/pa-files/PA-10-026.html)

FOR THE LATEST INFORMATION ABOUT NCI INITIATIVES, VISIT

Division of Extramural Activities, National Cancer Institute
http://deainfo.nci.nih.gov/funding.htm

Center for Strategic Scientific Initiatives (CSSI)

The Center for Strategic Scientific Initiatives (CSSI) is an operating entity within the NCI Office of the Director. Its mission is to create and uniquely implement exploratory programs focused on the development and integration of advanced technologies, trans-disciplinary approaches, infrastructures, and standards to accelerate the creation of publically available, broadly accessible, multi-dimensional data, knowledge, and tools to empower the entire cancer research continuum and ultimately augment patient benefits. Listed below are select programs, and their associated funding opportunities, within CSSI's six offices relevant to this workshop on detection, diagnostics, and technology development. For more information visit: http://cssi.cancer.gov.

Office of Biorepositories and Biospecimens Research (OBBR)

- The **Innovative Molecular Analysis Technologies (IMAT) program** supports investigator-initiated technology development projects that have the potential for revolutionizing cancer research and medicine. As a trans-divisional at the NCI program, IMAT provides support for the development of technologies from their inception to validation; accelerating the research of cancer biology, prevention, treatment and diagnosis, control and epidemiology, and cancer health disparities. Mechanisms of support include RFAs in areas of Innovative Technology Development for Cancer Research, Emerging Technology Development for Cancer Research, and Innovative and Applied Emerging Technologies in Biospecimens Science. For more information visit: http://innovation.cancer.gov.

Office of Cancer Clinical Proteomics Research (OCCPR)

- The **Clinical Proteomic Technologies for Cancer (CPTC) initiative** was launched in 2006 to address both the need for an evidence-based, proteomics pipeline and to address the other barriers in the field of proteomics. This initiative is focused on removing technical barriers in order to enable the accurate, efficient, and reproducible identification and quantification of a meaningful number of proteins to drive clinically-relevant biomarker qualification studies. The main goals of the initiative are:

    - To assist the proteomics community in designing appropriate studies related to the clearance/approval of multiplexed protein-based In Vitro Diagnostics (IVD) proteomic platforms. Two mock 510(k) pre-submissions along with the comments from the FDA review staff were developed and published. These documents helped streamline the regulatory process by providing examples of submission formatting, and provide a framework for the future development of similar public documents.

    - To aid the research community with access to highly characterized monoclonal antibodies. On the basis of discussions with the cancer research community, an Antibody Characterization Program (http://antibodies.cancer.gov) was developed by OCCPR. This public resource of renewable antibodies against cancer-associated target proteins produces well-characterized monoclonal antibodies along with publicly accessible Standard Operating Procedures, and it is beginning to address the lack of highly characterized reagents and resources currently available.

  In a pilot effort to link outputs of genome to proteome, the next phase of CPTC will partner with The Cancer Genome Atlas (TCGA) to comprehensively delineate the proteins that derive from modulations and aberrations in the human cancer genomes and related biological processes, and to provide this data with accompanying assays and biologically relevant knowledge as a public resource to be applied by researchers in larger-scale clinical validation studies. For more information visit: http://proteomics.cancer.gov.

Office of Cancer Nanotechnology Research (OCNR)

- The **NCI Alliance for Nanotechnology in Cancer program** is a comprehensive, systematized initiative encompassing the public and private sectors, designed to accelerate the application of nanotechnology to develop new strategies for the early diagnosis and treatment of cancer. Currently, scientists are limited in their ability to turn promising molecular discoveries into benefits for cancer patients. Nanotechnology can provide the technical power and tools that will enable those developing new diagnostics, therapeutics, and preventives to accelerate their transformation into cancer-relevant applications in clinical practice. For more information visit: http://nano.cancer.gov.

Office of Physical Sciences-Oncology (OPSO)

- The **Physical Sciences-Oncology Centers (PS-OCs) Program** was launched in September 2009. Expert teams working closely together from the fields of physics, chemistry, mathematics, engineering, cancer biology and oncology compose the PS-OC Network. The strategic goal of the program is to have the PS-OCs, both individually and collectively, cultivate a new trans-disciplinary environment and research that (1) originates and tests novel, non-traditional physical sciences-based approaches to understanding and controlling cancer; (2) generates orthogonal sets of physical measurements and integrates them with existing knowledge of cancer; and (3) develops and evaluates theoretical physics approaches to provide a comprehensive and dynamic picture of cancer. The PS-OC Program fosters the development and testing of pioneering approaches and stimulates new fields of study based on the convergence of biological and physical sciences, leading to a greater understanding of cancer behavior and processes and ultimately using this knowledge to treat and prevent cancer.

- A second initiative is a collaborative interagency partnership between NCI OPSO and the National Science Foundation (NSF) named the **Physical/LIfe Sciences Early-Stage Research (PLIER)** Awards, which was launched in July 2011. The PLIER Awards is based on a shared view by both agencies that significant advances may be expected as the result of continued investments in inter-and multi-disciplinary research at the intersection of the engineering/physical sciences and the life sciences, with a focus on advancing the fundamental understanding of cancer biology to underpin translational research promoting the prevention, detection, and treatment of cancer. For more information visit: http://opso.cancer.gov.

FUNDING OPPORTUNITIES IN CSSI

Nanoscience and Nanotechnology in Biology and Medicine (R01/R21) PA-11-148 & PA-11-149
Purpose: The objective of this FOA is to encourage the study of basic biological phenomena and engineer nanotechnology solutions that will enable biomedical breakthroughs in the diagnosis, treatment, and management of diseases and traumatic injuries. Piotr Grodzinski, Ph.D., Director, OCNR, grodzinp@mail.nih.gov, (301) 451-8983.

PS-OC Pilot Projects and Outreach Pilot Projects: Visit the website of each NCI Physical Sciences – Oncology Center (PS-OC) to learn about their current funding opportunities. http://opso.cancer.gov/centers/

NSF/NCI PLIER Awards Program: The NCI/NSF co-sponsored Physical/LIfe Sciences Early-Stage Research (PLIER) Awards Program will solicit applications in the Fall 2011. Larry Nagahara, Ph.D., Director, OPSO, nagaharl@mail.nih.gov, (301) 451-3388.

IMAT RFAs: To be reissued in later in 2011/early 2012.

NCI FUNDING PROGRAMS

INNOVATIVE MOLECULAR ANALYSIS TECHNOLOGIES PROGRAM (IMAT)

The Innovative Molecular Analysis Technologies (IMAT) program supports investigator-initiated technology development projects that have the potential for revolutionizing cancer research and medicine. As a trans-divisional at the NCI program, IMAT provides support for the development of technologies from their inception to validation; accelerating the research of cancer biology, prevention, treatment and diagnosis, control and epidemiology, and cancer health disparities.

IMAT has three separate solicitations that cover three strategic interests

- **Innovative Technology Development for Cancer Research**
  - Emphasizes exploratory research projects focused on the inception and development of early stage, highly innovative, and high impact cancer technologies.
  - No preliminary or proof-of-concept data are required.

- **Emerging Technology Development for Cancer Research**
  - Emphasizes the development of a technology in a biological context relevant to its intended use
  - Two mechanisms to support 1) technology development pilot projects that explore its initial application or use and, 2) validation and advanced development of an emerging technology

- **Innovative and Applies Emerging Technologies in Biospecimen Science**
  - Emphasizes novel technologies to assess, evaluate, and interrogate biospecimens, or analytes thereof, in order to maximize their quality and utility
  - Two support mechanisms for 1) technology development pilot projects that explore its use in biospecimen/sample preparation and, 2) validation and advanced development

For more information: http://innovation.cancer.gov

ADDITIONAL NCI FUNDING PROGRAMS

Exploratory Studies in Cancer Detection, Diagnosis and Prognosis: PA-08-267 (R21)
Release/Posted Date: September 23, 2008; Expiration Date: September 8, 2012
Application Receipt Dates: February 16, June 16, October 16
The Cancer Diagnosis Program (CDP) and the Cancer Therapy Evaluation Program (CTEP) of the Division of Cancer Treatment and Diagnosis and the Cancer Biomarkers Research Group of the Division of Cancer Prevention, NCI encourage application submissions that involve the initial evaluation of new molecular or cellular characteristics of pre-malignant cells or tumors or the development of assays that will be useful for cancer detection, diagnosis, and/or prognosis. This grant program provides limited funds for short-term pilot projects or feasibility studies to support exploratory research. Contact: Dr. James V. Tricoli, CDP, 301-496-1591, E-mail: tricolij@mail.nih.gov, Dr. Roy Wu, CTEP, 301-496-8866, E-mail: wur@mail.nih.gov, or Dr. Karl Krueger, Division of Cancer Prevention, 301-594-1044, E-mail: kruegerk@mail.nih.gov

Biomarkers of Infection-Associated Cancers: PA-11-158(R01) & PA-11-159(R21) (Reissue of PA-08-156 & PA-08-157)
Release/Posted Date: April 22, 2008; Expiration Date: May 8, 2014
Application Receipt Dates: February 16, June 16, October 16 (R21) & February 5, June 5, October 5 (R01)
The goal of this FOA is to encourage research that will increase our knowledge of infectious agent-associated malignancies and utilization of molecular profiles in early detection, risk assessment, and prevention of cancer. Contact: Dr. Karl Krueger, Division of Cancer Prevention,301-435-1594, E-mail: kruegerk@mail.nih.gov; Dr. T. Kevin Howcroft, Division of Cancer Biology, 301-496-7815, E-mail: howcrofk@mail.nih.gov

Exfoliated Cells and Circulating DNA in Cancer Detection and Diagnosis: PA-09-238 (R21)
Release Date: July 22, 2009; Expiration Date: September 8, 2012
Application Receipt Dates: March 16, July 16, November 16
The purpose of this PA is to develop novel technologies for capturing, enriching, and preserving exfoliated abnormal tumor cells and macromolecules in body fluids or effusions and to develop methods for concentrating the content of such specimens that originated from tumor or a pre-neoplastic lesion for biomarker studies. In the context of this PA, the term "exfoliation" denotes not only the whole tumor cells, but also cellular materials, such as DNA and proteins. Contact: Dr. Lynn Sorbara, Division of Cancer Prevention, 301-435-0584, lynns@mail.nih.gov

Mitochondria in Cancer Epidemiology, Detection, Diagnosis and Prognosis (R01) PA-11 073
Mitochondria in Cancer Epidemiology, Detection, Diagnosis and Prognosis (R21) PA-11-074
Expiration Date: January 8, 2014
Purpose: Encourage applications to develop and validate new mitochondrial-related biomarkers for cancer early detection, diagnosis, prognosis, risk assessment, and response to preventive and ameliorative treatments

THE NIH BIOENGINEERING PROGRAM

The bioengineering program provides support for highly significant investigator-initiated bioengineering research projects that apply physical, engineering, or computational science principles to the study of biology, medicine, behavior, or health. The goal of the program is to advance fundamental concepts, create knowledge, and develop innovative biologicals, materials, processes, implants, devices, and informatics to aid in prevention, detection, diagnosis, and treatment of cancer. Investigators can apply for support of any stage of a project, from early research and concept development to major translational efforts. Both small and large-scale research projects are welcome.

The NCI is committed to advancing emerging technologies with the potential to increase the understanding of cancer biology and to enhance cancer prevention, detection, treatment and diagnosis, control and epidemiology.

The bioengineering program has three separate solicitations:

- **Exploratory/Developmental Bioengineering Research Grant (EBRG)**
    - Emphasizes early stage, highly innovative, high-risk, high pay-off projects
    - Projects focused on the inception and development of novel research approaches
    - No preliminary or proof-of-concept data are required.

Link: http://grants.nih.gov/grants/guide/pa-files/PA-06-418.html

- **Bioengineering Research Grant (BRG)**
    - Emphasizes highly innovative discovery, developmental, hypothesis- or non-hypothesis-driven research.
    - Explore new research paradigms, or represent new concepts that combine bioengineering, physical, and biological/clinical sciences

Link: http://grants.nih.gov/grants/guide/pa-files/PA-07-279.html#SectionV

- **Bioengineering Research Partnerships (BRP)**
    - Emphasizes large scale multi-disciplinary collaborations and partnerships among the allied quantitative and biomedical disciplines. BRP projects may propose research that could lead to a novel device as a products

Link: http://grants.nih.gov/grants/guide/pa-files/PAR-07-352.html

Office of International Affairs

The Office of International Affairs (OIA) focuses on **building capacity for research and cancer control.** The focus of OIA's activities in capacity building for research and cancer control is assistance to low- and middle-income countries (LMICs). In addition to training in National Cancer Institute (NCI) intramural laboratories, supported under the NIH Visiting program, OIA) partially supports training of scientists from low- and middle-income countries in U.S. intramural and extramural NCI-supported laboratories. Specifically, OIA is charged with:

- Coordinating, planning, management, and evaluation of the international research, control, and information activities of the National Cancer Program
- Serving as the NCI focal point with the Fogarty International Center, The Office of Global Affairs of the Department of Health and Human Services, the State Department and other Federal organizations involved in international health activities
- Coordinating cancer activities under formal and informal collaborative agreements between the United States and other countries

Short-term Scientist Exchange Program

The Office of International Affairs (OIA) Short-Term Scientist Exchange Program (STSEP) promotes collaborative research between established U.S. and foreign scientists from low, middle, and upper-middle income countries by supporting, in part, exchange visits of cancer researchers from foreign laboratories. Visits of U.S. scientists to overseas laboratories in these countries are also considered for support. The visits may be from one week to six months in duration. Candidates must have a Ph.D., M.D., or a certified equivalent degree, a minimum of one year postdoctoral experience in cancer research, and an invitation from a qualified host. Awardees must fulfill the visa requirements of the host country.

The program's objective is to facilitate interactions between American and foreign scientists, and to promote sustainable collaborations. Although exchange visits between two non-U.S. countries are not supported under the STSEP, the Program actively encourages direct exchanges of both foreign and US-based scientists.

Summer Curriculum in Cancer Prevention

Each year, individuals from both high-income and a number of LMICs participate in the *NCI Summer Curriculum in Cancer Prevention*. Participants from LMICs receive partial or full scholarships to cover travel and subsistence from OIA. In the period 2003 to 2010, sponsored participants totaled over 300 individuals from about 70 LMICs. In some instances, these participants in the Summer Curriculum represent the only interaction between NCI and their country. In the past several years, OIA has actively partnered with the International Atomic Energy Agency (a UN agency active in cancer control in LMICs) to identify candidates for the Summer Curriculum. One "target" for these activities is sub-Saharan Africa. Approximately one-third of the participants for the past several years (including 2011) are from sub-Saharan Africa. More information and application materials for the Summer Curriculum are available at http://www3.cancer.gov/prevention/pob.

Further information on OIA programs can be found at http://oia.cancer.gov/

FOGARTY
INTERNATIONAL CENTER

Information and Funding Opportunities

THE FOGARTY INTERNATIONAL CENTER

Mission: The Fogarty International Center (FIC) is dedicated to advancing the mission of the National Institutes of Health by supporting and facilitating global health research conducted by U.S. and international investigators, building partnerships between health research institutions in the U.S.and abroad, and training the next generation of scientists to address global health needs.

FIC Strategic Plan: Pathways to Global Health Research

- Address the growing epidemic of chronic, non-communicable diseases
- Bridge the implementation research training gap
- Develop human capital in the developing world
- Foster a sustainable research environment in low- and middle-income countries
- Build strategic alliances and funding partnerships

Division of International Training and Research (DITR)
Administers research grants, research training grants, and fellowship programs at sites in more than 100 countries. Fogarty programs that build the research pipeline are anchored to peer-reviewed research grants and designed to be collaborative, long term and flexible. Nearly a quarter of Fogarty awards are made directly to robust research institutions in the developing world. The remaining grants support scientists at U.S. institutions who collaborate with colleagues abroad. About one-third of Fogarty's grants focus on scientific discovery, and two-thirds support research training.

Division of International Science Policy, Planning, and Evaluation (DISPPE)
Provides strategic information and guidance to the Fogarty Director regarding the planning and evaluation of programs at the Center. The division advises Fogarty and its Director on matters of international science policy, legislation and partnerships. DISPPE tracks activities of international funding agencies and research trends in global health.

Division of International Relations (DIR)
Develops new partnerships between U.S. scientists, institutions and counterparts abroad to advance research and training in the biomedical and behavioral sciences. DIR works on behalf of Fogarty and the whole of NIH to identify opportunities for collaboration with foreign science funding agencies, the U.S. Department of State, U.S. technical agencies and international organizations.

Division of International Epidemiology and Population Studies (DIEPS)
Conducts research in epidemiology and mathematical modeling of infectious diseases. Primary concentrations include cross-national studies of mortality patterns with special emphasis on influenza-associated disease, malaria and other vector-borne and vaccine-preventable diseases. Outcomes of DIEPS research and other activities are changes in public health policies and practices to decrease disease burdens.

http://www.fic.nih.gov

FOGARTY INTERNATIONAL CENTER

FUNDING OPPORTUNITIES

Visit http://www.fic.nih.gov/Programs/Pages/default.aspx for further information on these programs

Non-Communicable Disease Research Training Award (NCD-Lifespan) – D43
Receipt date(s): September 21, 2011; September 21, 2012
Purpose: To support collaborative research training between institutions in the U.S. and low-and middle-income countries (LMIC). The research training program is expected to train in-country experts to conduct research on non-communicable diseases, with the ultimate goal of implementing evidence-based interventions relevant to their countries.

International Tobacco and Health Research and Capacity Building Program (Tobac) – R01
Receipt date(s): September 15, 2011
Purpose: Aims to encourage trans-disciplinary research in the tobacco epidemic and to reduce the global burden of morbidity and mortality caused by tobacco use. It also aims to strengthen the research base of the U.S. and foreign institutions, especially those in LMICs.

International Research Ethics Education & Curriculum Development Award (Bioethics) – R25
Receipt date(s): May 10, 2012
Purpose: To develop Masters level curricula and provide educational opportunities for developing country academics, researchers, and health professionals in ethics related to performing research involving human subjects in international resource poor settings.

Fogarty International Research Collaboration Award (FIRCA) – R03
Receipt date(s): January 10, 2012; January 10, 2013
Purpose: To foster international research partnerships between NIH-supported scientists and their collaborators in low- and middle-income countries (LMIC). The FIRCA program aims to benefit the research interests of both collaborators while increasing and enhancing research capacity at the LMIC site.

Global Research Initiative Program for New Foreign Investigators (GRIP) – R01
Receipt date(s): March 9, 2012; March 8, 2013
Purpose: To promote productive development of foreign investigators from LMICs trained in the U.S. or in their home countries through an eligible NIH funded research or research training grant or award. The goal of this initiative is to provide research funding opportunities upon their return home to advance critical issues in global health when they return home.

International Research Scientist Development Award (IRSDA) – K01
Independent Scientist in Global Health Award (ISGHA) – K02
Receipt date(s): March 1, 2012
Purpose: To foster the development of outstanding junior (K01) and independent scientists (K02) and enable them to expand their potential to make significant impact on the health related research needs of LMICs.

Japan Society for the Promotion of Science Fellowship Opportunities (JSPS)
Receipt date(s): Varies
Purpose: JSPS, as the funding agency, provides two main types of scientific collaboration fellowships using the NIH as a nominating authority. The Intramural Fellowship program allows Japanese scientists to conduct research at NIH. The remaining Extramural Fellowships allow U.S. (and permanent resident) scientists to conduct cooperative research under their host researchers in Japan.

FOR THE LATEST INFORMATION ABOUT NCI INITIATIVES VISIT

http://www.cancer.gov/researchandfunding/announcements

Contact Information for Attendees

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Abaffy, Tatjana	University of Miami	tabaffy@med.miami.edu
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